16.1.1 Final Protocol and Protocol Amendments

16.1.1.1 C4591001 PACL 11Jan2023 (CT02-GSOP-RF16 8.0)_2_54 (1)

16.1.1.2. C4591001 Protocol Amendment 20, 15 September 2022

16.1.1.3. C4591001 Protocol Amendment 19, 21 March 2022

16.1.1.4. C4591001 Protocol Amendment 18, 07 September 2021

16.1.1.5. C4591001 Protocol Amendment 17, 20 July 2021

16.1.1.6. C4591001 Protocol Amendment 16, 28 May 2021

16.1.1.7. C4591001 Protocol Amendment 15, 25 March 2021

16.1.1.8. C4591001 Protocol Amendment 14, 02 March 2021

16.1.1.9. C4591001 Protocol Amendment 13, 12 February 2021

16.1.1.10. C4591001 Protocol Amendment 12, 14 January 2021

16.1.1.11. C4591001 Protocol Amendment 11, 04 January 2021

16.1.1.12. C4591001 Protocol Amendment 10, 01 December 2020

16.1.1.13. C4591001 Protocol Amendment 9, 29 October 2020

16.1.1.14. C4591001 Protocol Amendment 8, 15 October 2020

16.1.1.15. C4591001 Protocol Amendment 7, 06 October 2020

16.1.1.16. C4591001 Protocol Amendment 6, 08 September 2020

16.1.1.17. C4591001 Protocol Amendment 5, 24 July 2020

16.1.1.18. C4591001 Protocol Amendment 4, 30 June 2020

16.1.1.19. C4591001 Protocol Amendment 3, 10 June 2020

16.1.1.20. C4591001 Protocol Amendment 2, 27 May 2020

16.1.1.21. C4591001 Protocol Amendment 1, 13 May 2020

16.1.1.22. C4591001 Protocol, 15 April 2020

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19e068cb5\Approved\Approved On: 25-Jul-2023 08:04 (GMT)

11-Jan-2023

RE: Protocol Administrative Changes and Clarifications for Study C4591001 A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Dear Investigator,

This Protocol Administrative Change Letter (PACL) is to notify you of the following administrative changes and clarifications to the C4591001 protocol: Final Protocol Amendment 20, dated 15 September 2022. This administrative change is applicable only to site 1241.

The planned change is not considered substantial by Pfizer Inc. because there is no significant impact to the safety or physical or mental integrity of the trial participant, the scientific value of the trial, the conduct or management of the trial, or the quality or safety of any investigational medicinal product used in the trial, and therefore is not part of a formal amendment.

The following change relates to wording in Sections 8, 8.11, and 8.13 of Protocol Amendment 20. After appropriate approvals have been received at the site level either an in-person or telephone final contact will be permissible at site 1241 for the purpose of informing study participants of early study completion. If an in-person contact is completed, the same protocol guidance should be followed as for telephone contact:

- Participants will be informed of the changes brought about by protocol amendment 20, participants within the mandatory adverse event (AE) reporting period will have up-to-date AE data collected and
- Participants will have their final disposition case report form (CRF) completed to conclude their study participation.
- No further data will be collected after that point, and no further study visits or procedures should be completed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19db7a6a2\Approved\Approved On: 13-Jun-2023 07:32 (GMT)

DocUUID : e420c547-dc72-4e8b-ac21-9620a8aebfe0

If the protocol requires substantial changes in the future that apply globally to all sites, the non-substantial changes described in this letter will be incorporated into the amended protocol.

Review/approval by institutional review board/ethics committee (IRB/EC) is not required prior to PACL implementation. Please inform your IRB/EC of these changes, as required.

Sincerely,

PPD

14 Jan 2023 08:30:008-0500

PPD

cc: Trial Master File

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

090177e19db7a6a2\Approved\Approved On: 13-Jun-2023 07:32 (GMT)

DocUUID : e420c547-dc72-4e8b-ac21-9620a8aebfe0

1 ✓

Subject CN	TAIGLE LLC
Subject DN	EMAILADDRESS=operations@msbdocs.com,CN=TAIGLE LLC,OU=MSB,O=TAIGLE LLC,L=Irvine,ST=California,C=US
Email	operations@msbdocs.com
Serial #	132378441527873428230597372186267991 46
Issuer DN	CN=Entrust Class 3 Client CA - SHA256,OU=(c) 2015 Entrust, Inc. - for authorized use only,OU=See www.entrust.net/legal-terms,O=Entrust, Inc.,C=US
Signing Time	14 Jan 2023 08:30:008-0500

✓ The Certificate chain was successfully built to a Trusted Root Certificate.

✓ The Signer's identity is valid.

✓ The Document has not been modified since the signature was applied.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19db7a6a2\Approved\Approved On: 13-Jun-2023 07:32 (GMT)

This page was added to the original document by the MSB Validation Service (SVS) as part of the process to convert active signature block content into inactive text. A full validation report of each signature is generated and cross-referenced using a numeric footnote annotation.

DocUUID : e420c547-dc72-4e8b-ac21-9620a8aebfe0

Audit Trail Report

Document Name: C4591001 PACL 11Jan2023 (CT02-GSOP-RF16 8.0)_2_54.pdf

Document ID: e420c547-dc72-4e8b-ac21-9620a8aebfe0

Time Stamp	User	Action	Details
13 Jan 2023 17:14:011-0500	PPD UUID : PPD Email PPD IP Address : PPD	Started	The custodian composed the ePak succesfully. Subject: C4591001 PACL 11Jan2023 (CT02-GSOP-RF16 8.0)_2_54 ePak UUID: PPD
13 Jan 2023 17:14:011-0500	PPD UUID : PPD Email : PPD	RequestSent	Sign request sent to ePak recipient.
14 Jan 2023 08:29:041-0500	PPD UUID : PPD Email : PPD IP Address : PPD	DocumentViewed	Document viewed by signer.
14 Jan 2023 08:30:008-0500	PPD UUID : PPD Email : PPD IP Address : PPD	SignerTagFilled	The signer filled Time Stamp. Value: 14 Jan 2023 08:30:008-0500
14 Jan 2023 08:30:008-0500	PPD UUID : PPD Email PPD IP Address : PPD	Signed	The recipient signed the document with no comments. Comments: None Reason: None Consent: I understand that my Electronic Signature is Equivalent to my Handwritten Signature and is therefore legally binding. My Electronic Signature will remain unique to me, and under no circumstance I am allowed to disclose my password to any individual which may allow unauthorized access to system. I understand that I am accountable and responsible for all actions associated with my Electronic Signature.
14 Jan 2023 08:30:008-0500	PPD UUID PPD Email : PPD	Completed	The ePak is completed successfully.

090177e19db7a6a2\Approved\Approved On: 13-Jun-2023 07:32 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

ema.europa.eu

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**

Protocol amendment 20	15 September 2022	• Added language pertaining to early completion of this clinical trial as agreed with FDA and EMA.
		  • Updated schedules of assessments and protocol text to identify study visits that no longer need to be completed.
		  • Updated Study Procedures to describe site actions following approval of protocol amendment 20.
		• Removed the objective to describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2" because of the volume of BNT162b2 now distributed and administered globally using manufacturing "Process 2," making this comparison unwarranted.
		  • Removed corresponding endpoints.
		  • Removed corresponding wording throughout the protocol text.
		  • Added rationale for removal of this objective.
		• Added wording regarding return of e-diary devices or removal of application from participants' personal devices at the end of the study.

Protocol amendment 19	21 March 2022	• Inclusion of an additional 30-µg dose of BNT162b2 for eligible participants from protocol amendments 13-15 who received at least 3 doses of BNT162 in the study.
		  • Added corresponding objectives, estimands, and endpoints.
		  • Added corresponding SoA and procedures.
		  • Added details in the statistical methods sections.
		• Added language to permit early discontinuation of participants for reasons including but not limited to the increased access and availability of BNT162b2 in the real world, reducing the value of participant involvement and observation in this clinical trial.
		• Updated the eligibility window for participants to receive the third (booster) dose under protocol amendment 18 from at least 6 months after Dose 2 to at least 3 months after Dose 2 to provide maximum opportunity to all participants to receive the third dose.
		• Updated the existing objectives, estimands, and endpoints in line with the revised schedule and study duration, and where applicable, removed what is no longer relevant.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified AE/SAE collection requirements for participants enrolled under protocol amendments 18 and 19. • Updated risk assessment as BNT162b2 is no longer a novel vaccine and there are extensive data available from both clinical trial and real-world settings.

Protocol amendment 18	07 September 2021	• Addition of procedures for monitoring potential myocarditis or pericarditis.
		• Addition of a third dose of BNT162b2 for participants who meet specified recommendations and have not yet received a third dose.
		  • Added corresponding objectives, estimands, and endpoints.
		  • Added corresponding SoA and procedures.
		  • Added details in the statistical methods sections.
		• Added the instruction that participants who receive COVID-19 vaccines outside of the study from protocol amendment 18 onwards should be withdrawn.

Protocol amendment 17	20 July 2021	• Changed the analysis method for the within-group comparison of seroresponse rates for Phase 3 booster and VOC immunogenicity assessment from the Miettinen and Nurminen method to the adjusted Wald interval to provide tighter CI and higher power for NI in most cases. • Clarified that any nonstudy coronavirus vaccines are to be recorded at any time they are given during study participation. • Clarified that participants who are randomized in the C4591031 study should be withdrawn from this study.
Protocol amendment 16	28 May 2021	• Removed the requirement to conduct a potential COVID-19 convalescent visit following each potential COVID-19 illness visit. • Clarified that only non-Pfizer interventional studies for prevention of COVID-19 are prohibited throughout study participation. • Clarified that during the 7 days following each vaccination (either as part of this study, co-enrolled C459 studies, or the B7471026 [20vPnC] study), potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Revised the noninferiority margin from 2-fold to 1.5-fold and added a minimum GMR point estimate of ≥0.8 as another success criterion for Phase 3 booster and VOC immunogenicity assessment. Noninferiority is met if the lower limit of the alpha-adjusted CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.8. • Added Phase 1 booster participants to the Dose 3 booster immunogenicity population definitions. • Included a booster safety population definition. • Clarified that the interim analyses for booster immunogenicity will be conducted when serology data for the reference strain or for the SA strain are available.
Protocol amendment 15	25 March 2021	• In order to further characterize booster responses induced by BNT162b2, 2 additional lower-dose booster groups have been added to the subset for evaluation of boostability and protection against emerging VOCs. An additional 5-µg or 10-µg dose of BNT162b2 will be given to approximately 144 Phase 3 participants approximately 5 to 7 months after their second dose of BNT162b2. • To further describe cell-mediated immune responses following isolations of PBMCs in a subset of both the Phase 3 participants who receive a single booster vaccination and the BNT162b2-naïve group who receive BNT162b2$_{SA}$, additional genetic testing may also be performed; corresponding details and an appendix have been added. • An exploratory objective was added for Phase 3 participants to describe the immune response to a third dose of BNT162b2 or a third or fourth dose of BNT162b2$_{SA}$ at later time points to align with analyses and corresponding changes detailed in the statistical section. • Removed the lower age limit for eligibility for administration of BNT162b2 to those originally assigned to placebo: this will now be covered in the recommendations detailed separately, and available in the electronic study reference portal. • Allowed administration of BNT162b2 at Visits 101 and 102 to pregnant participants in certain circumstances. • To align with contraception requirements, reduced the EDP reporting period to 28 days after the last dose of study intervention.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**

Protocol amendment 14	02 March 2021	• In order to further describe duration of protection, and heterologous/homologous protection against the emerging VOCs, an additional dose of BNT162b2 or BNT162b2$_{SA}$ will be given to approximately 600 Phase 3 participants approximately 5 to 7 months after their second dose of BNT162b2; a further dose of BNT162b2$_{SA}$ will be given to approximately 30 of those participants who receive BNT162b2$_{SA}$.
		  ◦ Added corresponding objectives, estimands, and endpoints
		  ◦ Added corresponding SoA and procedures
		  ◦ Added details in the statistical methods sections.
		• Approximately 300 BNT162b2-naïve participants will be enrolled and receive 2 doses of BNT162b2$_{SA}$ to describe heterologous/homologous protection against the emerging VOCs and reference strains:
		  ◦ Added corresponding objectives, estimands, and endpoints
		  ◦ Added corresponding SoA and procedures
		  ◦ Added details in the statistical methods sections.
		• Cell-mediated immune responses will also be described following isolations of PBMCs in a subset of both the Phase 3 participants who receive a single booster vaccination and the BNT162b2-naïve group who receive BNT162b2$_{SA}$
		• Added the asymptomatic case definitions in Section 8.1 and further clarified the secondary definition for asymptomatic case based on seroconversion of N-binding antibody.
		• Defined the analysis populations used for evaluation of asymptomatic infection based on seroconversion of N-binding antibody and based on NAAT from participants who consent to active surveillance.
		• Clarified that unblinding for a nonemergency reason should be conducted outside of the IRT system.
		• Clarified that if multiple visits occur on the same day, all procedures for all visits must be conducted (including collection of all blood samples).
		• Clarified the plan for stepwise unblinding of the sponsor in the study.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**

Protocol amendment 13	12 February 2021	• In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2:
		  • Added corresponding objectives, estimands, and endpoints
		  • Added corresponding SoA and procedures
		  • Added details in the statistical methods sections.
		• Clarified the population used for analysis of reactogenicity endpoints.
		• To align with current recommendations, investigators may exercise judgment on review of inclusion and exclusion criteria ahead of vaccination with BNT162b2 for participants who originally received placebo.
		• Clarified that if a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent.
		• Participants who provide biweekly swabs for surveillance of asymptomatic infection should now continue to swab even after unblinding if they originally received BNT162b2, to maximize the numbers of swabs to be collected.
		• Clarified the procedures for unscheduled visits to administer a second dose in the event a participant received only 1 dose of BNT162b2.

Protocol amendment 12	14 January 2021	• Because of a formatting error in protocol amendment 11, exclusion criterion 4 was inadvertently added to exclusion criterion 3 and the subsequent criteria renumbered. This amendment corrects that error. • Because of a change in the pace with which participants ≥16 years of age who originally received placebo will become eligible for receipt of BNT162b2, text was updated throughout the protocol to reflect that this will happen in a phased manner, with recommendations detailed separately and available in the electronic study reference portal. • Clarified that participants who are unblinded because they become potentially eligible for receipt of BNT162b2 will not participate in surveillance for asymptomatic SARS CoV-2 infection.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Corrected the exploratory objective to describe non-S seroconversion to SARS-CoV-2 to clarify that this will only include participants who received BNT162b2 at initial randomization (since those who received it subsequently do not have blood drawn). • In line with current recommendations, removed the requirement to discontinue study intervention because of a diagnosis of COVID-19 during the study.

Protocol amendment 11	04 January 2021	• Added approaches to evaluate efficacy against asymptomatic SARS-CoV-2 infection:
		  • Added objectives, estimands, and endpoints, and statistical methods, for assessment via N-binding antibody seroconversion;
		  • Added a potential intensive surveillance period for nasal swabbing, for assessment via NAAT:
		  • Corresponding objectives, estimands, and endpoints added
		  • Corresponding SoA and procedures added
		  • Details added in the statistical methods sections.
		• Added the possibility of assessing full-length S-binding, instead of S1-binding, IgG levels in Phase 2/3.
		• Clarified in Section 4.1.1 that any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity at the approximate time participants in Phase 2/3 reach Visit 4, for consistency with other sections.
		• Added a sentence to reflect that assent is obtained from participants <18 years of age.

Protocol amendment 10	01 December 2020	• Added the possibility of administering BNT162b2 to participants who originally received placebo, following any local or national recommendations. • Added the possibility of administering BNT162b2 to participants who originally received placebo, following completion of the active safety surveillance period. • Added corresponding exploratory objectives and statistical analysis details. • Removed immunogenicity analyses of titers greater than defined threshold(s). • Removed the need for blinded COVID-19 case review after the final efficacy analysis. • Included the possibility, due to local circumstances related to the COVID-19 pandemic, that study

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		procedures that do not require in-person participant contact may be performed by telehealth. • In light of additional information to better estimate the standard deviation of SARS-CoV-2 neutralizing titers, increased the sample size for the noninferiority immunogenicity analysis in adolescents 12 to 15 years of age.
Protocol amendment 9	29 October 2020	• To better align with the natural history of SARS-CoV-2 infection, added Phase 2/3 secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days after the second dose; also modified the existing secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days, as well as 7 days, after the second dose; • Made corresponding changes to the study design, study assessments and procedures, and statistical analysis sections. • For operational reasons, removed the interim analysis planned after accrual of 32 cases. • Clarified that interim analyses will be conducted after accrual of *at least* 62, 92, and 120 cases. • Included any participants 16 through 17 years of age enrolled under this amendment in the reactogenicity subset. • Added an unblinded clinical scientist to support DMC activities. • Clarified that serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.
Protocol amendment 8	15 October 2020	• Removed “N-binding antibody” and “SARS-CoV-2 detection by NAAT” as endpoints from the third exploratory objective, as these results are used for the determination of the population, and are not endpoints. • Clarified that the “Process 1” participants included in the descriptive analysis of “Process 1”- and “Process 2”-manufactured study interventions will be selected randomly. • Clarified that surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study. • Further modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified that for participants who are not in the reactogenicity subset, local reactions and systemic events following vaccination should be detected and reported as AEs. • Clarified that premenarchal females are not WOCBP. • Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2. • Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2." • Clarified the degree of unblinding on the unblinded submissions team in Section 6.3.3. • Made provision for a second dose of BNT162b2 in participants who were affected by a medication error at Visit 2 in Section 6.6. • Provided further clarification regarding discontinuation of study intervention in Section 7.1. • Modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Added that 2 periods of potential COVID-19 symptoms within 4 days will be considered as a single illness. • Provided guidance in Section 8.13 regarding circumstances in which a SARS-CoV-2 test might be required even if symptoms within 7 days following each vaccination are considered more likely due to vaccine reactogenicity. • Made allowance in Section 8.13 for a second SARS-CoV-2 test to be performed within the same potential COVID-19 illness if it is in accordance with routine practice. • Added Section 8.15 to describe the reporting of SARS-CoV-2 test results and their implications for participants receiving a second vaccine dose.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Added statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age. • Amended scope of analyses of safety data in Section 9.5.1. • Made various editorial changes.
Protocol amendment 6 (Germany-specific)	23 September 2020	• According to regulatory request, inclusion criterion 1 now specifies that participants less than 18 years of age will not be enrolled in the EU.
Protocol amendment 6	08 September 2020	• Reordered some procedures in the Phase 2/3 schedule of activities for consistency with the main body of the protocol. • Corrected the window for the 6-month follow-up visit to be approximately 6 months after Vaccination 2. • Reduced the volume of blood draws to ~20 mL. • Removed the need to have safety data reported for participants to be included in the safety objective assessment. • Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease. • Increased the sample size for Phase 2/3 to ~43,998. • Clarified that inclusion criterion 4 (ie, participants at higher risk for acquiring COVID-19) is applicable for Phase 2/3 only, and provided some examples. • Removed exclusion criterion 2 (ie, known infection with HIV, HCV, or HBV) for Phase 3 and added criteria for HIV-positive participants. • Decreased the lower age limit and removed the upper age limit for inclusion in Phase 2/3 in order to evaluate BNT162b2 30 µg in older adolescents and those over 85 years of age; updated the title and other references to adults to align with this change. • Renamed the immunological assays to align with other program-level documents. • Removed reference to the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) being “heads up.” • Clarified that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention. • Added clarification that potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Updated the analysis population descriptions to align with the study SAP.
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory. • Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7. • Updated the stopping and alert rule parameters for enhanced COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation, and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol. • To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• To permit individual and group dosing alterations for the second dose of study intervention Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial • Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 24
LIST OF FIGURES 25
1. PROTOCOL SUMMARY 26
1.1. Synopsis 26
1.2. Schema 40
1.3. Schedule of Activities 41
1.3.1. Phase 1 41
1.3.2. Phase 2/3 48
1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo 52
1.3.4. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) (Subset for Evaluation of Boostability and Protection Against Emerging VOCs) 54
1.3.5. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants 57
1.3.6. Surveillance for Asymptomatic SARS-CoV-2 Infection 60
1.3.7. Administration of a Third Dose of BNT162b2 to Participants Who Have Not Previously Received a Third Dose 61
1.3.8. Administration of a Fourth (or Fifth) Dose of BNT162b2 to Eligible Participants From Protocol Amendments 13, 14, and 15 63
2. INTRODUCTION 66
2.1. Study Rationale 66
2.2. Background 66
2.3. Clinical Overview 69
2.4. Benefit/Risk Assessment 69
2.4.1. Risk Assessment 70
2.4.2. Benefit Assessment 71
2.4.3. Overall Benefit/Risk Conclusion 71
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 72
3.1. For Phase 1 72
3.2. For Phase 2/3 74
4. STUDY DESIGN 80
4.1. Overall Design 80

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof once approved.

4.1.1. Phase 1 81
4.1.2. Phase 2/3 83
4.2. Scientific Rationale for Study Design 86
4.3. Justification for Dose 87
4.4. End of Study Definition 88
5. STUDY POPULATION 88
5.1. Inclusion Criteria 88
5.2. Exclusion Criteria 89
5.3. Lifestyle Considerations 92
5.3.1. Contraception 92
5.4. Screen Failures 92
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 93
6. STUDY INTERVENTION 93
6.1. Study Intervention(s) Administered 94
6.1.1. Manufacturing Process 95
6.1.2. Administration 95
6.2. Preparation/Handling/Storage/Accountability 96
6.2.1. Preparation and Dispensing 97
6.3. Measures to Minimize Bias: Randomization and Blinding 98
6.3.1. Allocation to Study Intervention 98
6.3.2. Blinding of Site Personnel 98
6.3.3. Blinding of the Sponsor 99
6.3.4. Breaking the Blind 100
6.4. Study Intervention Compliance 101
6.5. Concomitant Therapy 101
6.5.1. Prohibited During the Study 102
6.5.2. Permitted During the Study 103
6.6. Dose Modification 103
6.7. Intervention After the End of the Study 104
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 104

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

7.1. Discontinuation of Study Intervention 104
7.2. Participant Discontinuation/Withdrawal From the Study 104
7.2.1. Withdrawal of Consent 106
7.3. Lost to Follow-up 106
8. STUDY ASSESSMENTS AND PROCEDURES 106
8.1. Efficacy and/or Immunogenicity Assessments 108
8.1.1. Efficacy Against COVID-19 108
8.1.2. Efficacy Against Asymptomatic SARS-CoV-2 Infection 110
8.1.2.1. Seroconversion of N-Binding Antibody 110
8.1.2.2. NAAT-Confirmed SARS-CoV-2 Infection 111
8.1.3. Vaccine-Induced Immunogenicity 111
8.1.4. Biological Samples 111
8.1.5. Surveillance for Asymptomatic SARS-CoV-2 Infection 112
8.2. Safety Assessments 112
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 113
8.2.2. Electronic Diary 113
8.2.2.1. Grading Scales 114
8.2.2.2. Local Reactions 114
8.2.2.3. Systemic Events 115
8.2.2.4. Fever 116
8.2.2.5. Antipyretic Medication 117
8.2.3. Phase 1 Stopping Rules 117
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 118
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 119
8.2.6. Pregnancy Testing 119
8.3. Adverse Events and Serious Adverse Events 119
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 120
8.3.1.1. Reporting SAEs to Pfizer Safety 121
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 122
8.3.2. Method of Detecting AEs and SAEs 122
8.3.3. Follow-up of AEs and SAEs 122

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

8.3.4. Regulatory Reporting Requirements for SAEs....122
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure....123
8.3.5.1. Exposure During Pregnancy....123
8.3.6. Exposure During Breastfeeding....124
8.3.6.1. Occupational Exposure....125
8.3.7. Cardiovascular and Death Events....125
8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs....125
8.3.9. Adverse Events of Special Interest....126
8.3.9.1. Lack of Efficacy....126
8.3.10. Medical Device Deficiencies....126
8.3.11. Medication Errors....126
8.4. Treatment of Overdose....127
8.5. Pharmacokinetics....128
8.6. Pharmacodynamics....128
8.7. Genetics....128
8.8. Biomarkers....128
8.9. Immunogenicity Assessments....128
8.10. Health Economics....128
8.11. Study Procedures....128
8.11.1. Phase 1....129
8.11.1.1. Screening: (0 to 28 Days Before Visit 1)....129
8.11.1.2. Visit 1 – Vaccination 1: (Day 1)....130
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)....132
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)....133
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)....135
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)....137
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)....138

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 139
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4) 140
8.11.1.10. Between Visits 8 and 9 140
8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2) 140
8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a) 142
8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a) 143
8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2 144
8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2 144
8.11.2. Phase 2/3 144
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 144
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 147
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2) 149
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2) 150
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 151
8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 151
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 152
8.13. COVID-19 Surveillance (All Participants) 153
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 154

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit) 156
8.14. Communication and Use of Technology 156
8.15. SARS-CoV-2 NAAT Results 156
8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo 157
8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2) 157
8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101) 159
8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102) 160
8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102) 160
8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102) 161
8.17. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) (Subset for Evaluation of Boostability and Protection Against Emerging VOCs) 162
8.17.1. Visit 301 – Vaccination 3: (150 to 210 Days After Visit 2) 162
8.17.2. Visit 302 – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 301) 164
8.17.3. Visit 303 – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 301) 165
8.17.4. Visit 304 – 1-Week Follow-up Visit (Vaccination 4): (6 to 8 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$ 166
8.17.5. Visit 305 – 1-Month Follow-up Visit (Vaccination 4): (28 to 35 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$ 167
8.17.6. Visit 306 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 301) 168
8.17.7. Visit 307 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 301) 168
8.18. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants 169
8.18.1. Visit 401 – Vaccination 1: (Day 1) 169
8.18.2. Visit 402 – Vaccination 2: (19 to 23 Days After Visit 401) 171

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

8.18.3. Visit 403 – 1-Week Follow-up Visit (After Vaccination 2): (6 to 8 Days After Visit 402) 173
8.18.4. Visit 404 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 402) 174
8.18.5. Visit 405 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 402) 174
8.18.6. Visit 406 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 402) 175
8.19. Surveillance for Asymptomatic SARS-CoV-2 Infection 175
8.19.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11 176
8.19.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection 177
8.20. Administration of a Third Dose of BNT162b2 to Participants Who Have Not Previously Received a Third Dose 177
8.20.1. Visit 501 – Third Dose of BNT162b2 178
8.20.2. Visit 502 – 1-Month Follow-up Telephone Contact: (28 to 35 Days After Visit 501) 179
8.20.3. Visit 503 – 6-Month Follow-up Telephone Contact: (175 to 189 Days After Visit 501) 180
8.20.4. Visit 504 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 501): 180
8.21. Administration of a Fourth (or Fifth) Dose of BNT162b2 to Eligible Participants From Protocol Amendments 13, 14, and 15 181
8.21.1. Visit 601 – Dose 4: (At Least 175 Days After Visit 301 or Visit 8a): Only For Those Participants Who Received Dose 3 at Visit 8a or Visit 301 181
8.21.2. Visit 602 – 1-Month Follow-up Telephone Contact: (28 to 35 Days After Visit 601) 183
8.21.3. Visit 603 – 6-Month Follow-up Telephone Contact: (175 to 189 Days After Visit 601) 183
8.21.4. Visit 604 – Dose 5: (At Least 175 Days After Visit 303): Only for the Subset of Participants Who Receive Dose 4 at Visit 303 184
8.21.5. Visit 605 – 1-Month Follow-up Telephone Contact: (28 to 35 Days After Visit 604) 185

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

8.21.6. Visit 606 – 6-Month Follow-up Telephone Contact: (175 to 189 Days After Visit 601) 186
8.22. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis 186
9. STATISTICAL CONSIDERATIONS 187
9.1. Estimands and Statistical Hypotheses 187
9.1.1. Estimands 187
9.1.2. Statistical Hypotheses 187
9.1.2.1. Statistical Hypothesis Evaluation for Efficacy 187
9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity 188
9.2. Sample Size Determination 189
9.2.1. Phase 1 189
9.2.2. Efficacy Against COVID-19 190
9.2.3. Efficacy Against Asymptomatic Infection 190
9.2.4. Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years 190
9.2.5. Boostability and Protection Against Emerging SARS-CoV-2 VOCs 191
9.2.6. Safety 192
9.3. Analysis Sets 193
9.4. Statistical Analyses 195
9.4.1. Immunogenicity Analyses 195
9.4.2. Efficacy Analyses 206
9.4.3. Safety Analyses 210
9.4.4. Other Analyses 213
9.5. Interim Analyses 213
9.5.1. Analysis Timing 216
9.6. Data Monitoring Committee or Other Independent Oversight Committee 217
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 219
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 219
10.1.1. Regulatory and Ethical Considerations 219
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 219
10.1.2. Informed Consent Process 220

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.1.3. Data Protection 221
10.1.4. Dissemination of Clinical Study Data 221
10.1.5. Data Quality Assurance 222
10.1.6. Source Documents 224
10.1.7. Study and Site Start and Closure 224
10.1.8. Sponsor's Qualified Medical Personnel 225
10.2. Appendix 2: Clinical Laboratory Tests 226
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 228
10.3.1. Definition of AE 228
10.3.2. Definition of SAE 229
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 231
10.3.4. Reporting of SAEs 234
10.4. Appendix 4: Contraceptive Guidance 235
10.4.1. Male Participant Reproductive Inclusion Criteria 235
10.4.2. Female Participant Reproductive Inclusion Criteria 235
10.4.3. Woman of Childbearing Potential 236
10.4.4. Contraception Methods 237
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 239
10.6. Appendix 6: Abbreviations 241
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 245
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection 248
10.9. Appendix 9: Genetics 249
11. REFERENCES 250

LIST OF TABLES

Table 1. Local Reaction Grading Scale 115
Table 2. Systemic Event Grading Scale 116
Table 3. Scale for Fever 117
Table 4. Power Analysis for Noninferiority Assessment 191

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 192
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility....214
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses....215
Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall....215
Table 9. Laboratory Abnormality Grading Scale 226
Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 246
Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 247

LIST OF FIGURES

Figure 1. Multiplicity Schema....189

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which continues to spread globally at high speed. To date, more than 392 million people have been infected with SARS-CoV-2 and >5.7 million have died, demonstrating an urgent need for efficacious vaccines.

Numerous COVID-19 vaccines are currently in development globally, and several candidate COVID-19 vaccines (eg, mRNA vaccines and adenovirus-vectored vaccines expressing the S protein) have been shown to be efficacious in the prevention of COVID-19 in clinical studies and are now available under temporary or emergency authorizations. BNT162b2, an RNA-based COVID-19 vaccine given as a 2-dose series administered 21 days apart, was shown to be safe and effective in a Phase 1/2/3 study and has received authorizations for temporary or emergency use or marketing authorizations in multiple countries and has been fully licensed for use in individuals 16 years of age and above in the US as of 23 Aug 2021.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 3 antigens:

BNT162b1 (variant RBP020.3): a modRNA encoding the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5);

BNT162b2 (variant RBP020.2): a modRNA encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9);

BNT162b2s01 (variant RBP020.11): a modRNA encoding the P2 S containing South Africa B.1.351 variant–specific mutations, hereafter referred to as BNT162b2$_{SA}$, as a representative variant of concern (VOC).

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and/or efficacy of these prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1 and 6 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults at least 6 months after the second dose of either BNT162b1 or BNT162b2	• GMCs/GMTs at the time of Dose 3, 7 days and 1 month after Dose 3, and 12 months after Dose 2 • GMFRs from before Dose 3 to 7 days and 1 month after Dose 3 and 12 months after Dose 2 • GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2 • GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2 given as a fourth dose at least 6 months after the third dose of BNT162b2 for participants who received a fourth dose as part of protocol amendment 19	In participants receiving a fourth dose of study intervention, the percentage of participants reporting: • AEs and SAEs from Dose 4 to 1 month after Dose 4	• AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
Approved
090177e19b5013fa\Approved On: 16-Sep-2022 12:22 (GMT)

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
are europa.eu

Objectives[a]	Estimands	Endpoints
To describe the safety and tolerability profile of BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants, or as 2 doses to BNT162b2-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 5 or 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2 given as a third dose at least 3 months after the second dose of BNT162b2 (or BNT162b2$_{SA}$) for participants who received a third dose as part of protocol amendment 18	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • AEs and SAEs from Dose 3 to 1 month after Dose 3	• AEs • SAEs
To describe the safety and tolerability profile of BNT162b2 given as a fourth (or fifth) dose at least 6 months after the third (or fourth) dose of BNT162b2 (or BNT162b2$_{SA}$) for participants who received a fourth (or fifth) dose as part of protocol amendment 19	In participants receiving a fourth (or fifth) dose of study intervention, the percentage of participants reporting: • AEs and SAEs from Dose 4 (or Dose 5) to 1 month after Dose 4 (or Dose 5)	• AEs • SAEs
Primary Immunogenicity ***BNT162b2-experienced participants***		
To demonstrate the noninferiority of the anti–reference strain immune response after a third dose of BNT162b2 at 30 µg compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Objectives[a]	Estimands	Endpoints
BNT162b2-naïve participants		
To demonstrate the noninferiority of the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
BNT162b2-experienced participants		
To demonstrate the noninferiority of the anti-SA immune response after a third dose of BNT162b2 at 30 µg compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
To demonstrate the noninferiority of the anti–reference strain immune response after 1 dose of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ and a third dose of BNT162b2 at 30 µg	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg	SARS-CoV-2 SA NT in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$ or the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ and the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate a statistically greater anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 SA NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
To descriptively compare the anti–reference strain immune response after 2 doses of BNT162b2$_{SA}$ and after 2 doses of BNT162b2	GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Objectives[a]	Estimands	Endpoints
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants after receipt of each dose of BNT162b2: Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT at baseline and 1 and 6 months after Dose 2 and GMFR from baseline to 1 and 6 months after Dose 2	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants) 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate and characterize the SARS-CoV-2 isolate in cases of: • Confirmed COVID-19 cases that occur through approximately 6 months after the second dose • Confirmed severe COVID-19 cases that occur through approximately 6 months after the second dose		• SARS-CoV-2 neutralizing titers • Identification of SARS-CoV-2 variant(s)
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the immune response to any VOCs not already specified	Geometric mean NT for any VOCs not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2	• SARS-CoV-2 NTs for any VOCs not already specified
To describe the immune response to a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$	• GMTs at Dose 3 and subsequent time points • GMFRs from Dose 3 to subsequent time points	• SARS-CoV-2 reference strain NTs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and SA in a subset of participants: • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 2 doses to BNT162b2-naïve participants • 7 Days and 1 and 6 months after BNT162b2 given as a third dose to BNT162b2-experienced participants		

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Participants who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ at 30 µg (based upon the South African variant and hereafter referred to as BNT162b2$_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

As part of protocol amendment 18, to reflect current and anticipated recommendations for COVID-19 vaccine boosters, participants in C4591001 who meet specified recommendations (detailed separately and available in the electronic study portal) and have not already received one, will be offered a third dose of BNT162b2 after their second dose of BNT162. This opportunity is only for those participants who received their first 2 doses of BNT162 (including BNT162b1, BNT162b2, or BNT162b2$_{SA}$) as part of the study.

As part of protocol amendment 19, eligible participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 will be offered an additional 30-µg dose of BNT162b2. BNT162-naïve participants who received 2 primary doses of 30 µg BNT162b2$_{SA}$ under protocol amendment 14 and were enrolled to receive a booster dose at Visit 501 under protocol amendment 18 are not eligible to receive an additional dose.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof are not peer reviewed.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

As part of protocol amendment 19, the study may be terminated early for reasons including but not limited to the increased access and availability of BNT162b2 in the real world, reducing the value of participant involvement and observation in this clinical trial. Further to this, participants who are offered the possibility to participate in a future study within the Pfizer/BioNTech COVID-19 vaccine development program will be discontinued from this study.

As of protocol amendment 20, because the study is now being fully unblinded with no control arm, making it observational in nature, and with the active safety surveillance period for the majority of participants completed, following agreement with the FDA and EMA, the study will be concluded early. Following approval of protocol amendment 20, active study participants will be informed of the early completion of the study and further data collection will be ceased.

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

For evaluation of boostability and protection against emerging VOCs, 600 existing Phase 3 participants 18 to 55 years of age will be rerandomized in a 1:1 ratio to receive either a third dose of BNT162b2 at 30 µg or a third dose of BNT162b2$_{SA}$.

An additional group of 30 existing Phase 3 participants 18 to 55 years of age will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$. For these 30 participants, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the investigator and sponsor will not be. Serum samples from these participants may be used for assay development purposes and, except for objectives relating to response to a fourth dose, their results will be analyzed separately from the main immunogenicity analyses.

A further group of approximately 144 existing Phase 3 participants 18 years of age and older will be enrolled to receive a third, lower, dose of BNT162b2 of either 5 or 10 µg. Approximately 24 participants 18 to 55 years of age and 48 participants >55 years of age will be enrolled in each dose group.

Three hundred participants 18 to 55 years of age who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19 will be enrolled as a new cohort of participants to receive BNT162b2$_{SA}$ given as a 2-dose series.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 5 µg, 10 µg, 20 µg, 30 µg
- BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S containing South Africa B.1.351 variant–specific mutations): 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3 or among participants that are offered the possibility of participating in another study within the Pfizer/BioNTech COVID-19 vaccine development program.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162.

Phase 1/2/3 participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 will be offered an additional dose of BNT162b2 at 30 µg at least 6 months after their last dose of BNT162b2 (or BNT162b2$_{SA}$).

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated. VE will be demonstrated if the lower bound of the 95% CI for VE is >20%.

In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

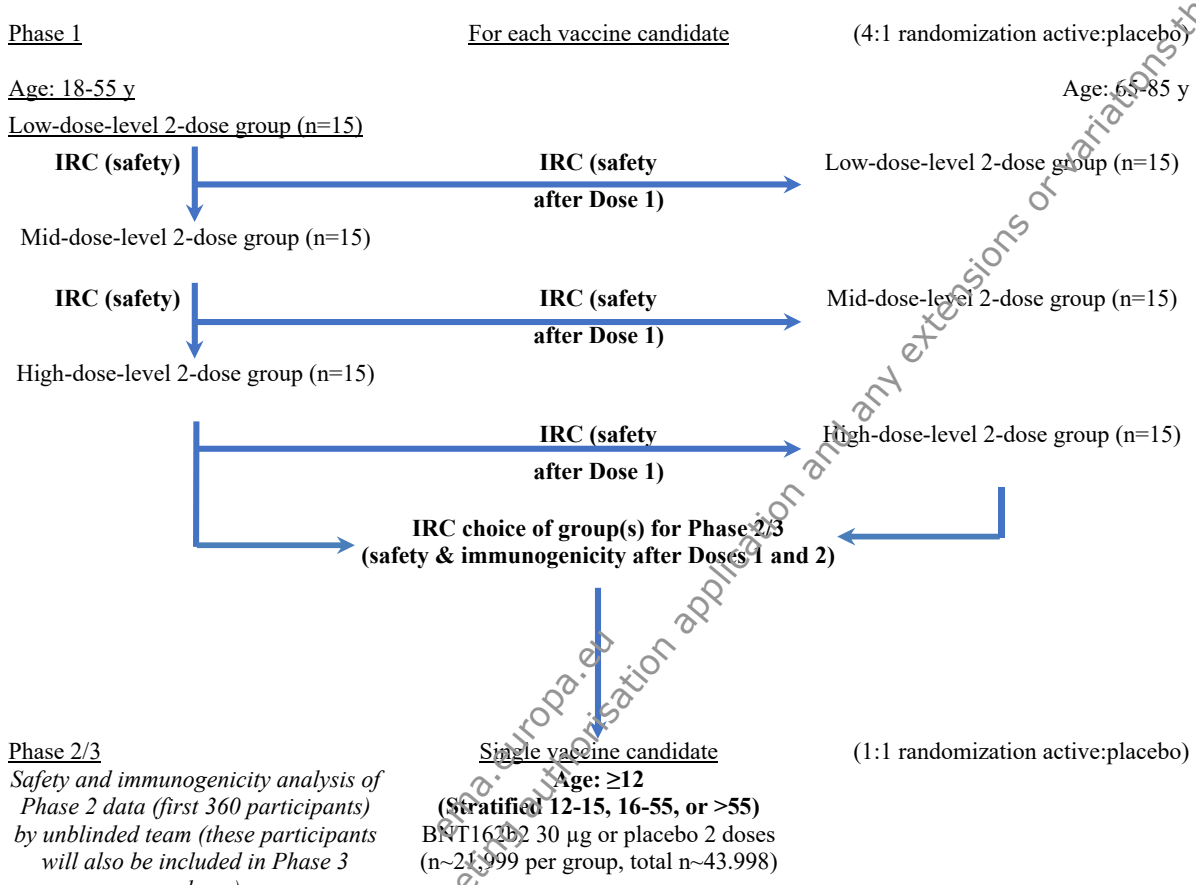
The boostability and protection against emerging VOCs for BNT162b2-experienced participants and BNT162b2-naïve participants will be assessed based on GMRs of SARS-CoV-2 SA-neutralizing and/or reference strain–neutralizing titers using a 1.5-fold noninferiority margin and the difference in percentages of participants with seroresponse using a 10% noninferiority margin.

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

Except for the objectives to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age and evaluation of boostability and protection against emerging VOCs by BNT162b2 and BNT162b2$_{SA}$ in Phase 3, the other immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMR, and the associated 95% CIs, for SARS-CoV-2 neutralizing titers, full-length S-binding or S1-binding IgG levels, and/or RBD-binding IgG levels (Phase 1 only) at the various time points.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

1.2. Schema



Abbreviation: IRC = internal review committee.

Note: Participants who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

1.3. Schedule of Activities

The SoA tables provide an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit is required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected. Prior to protocol amendment 16, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b1 or BNT162b2 (at any dose level) will continue in the study as originally planned.

All other participants will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study no later than at the approximate time participants in Phase 2/3 reach Visit 4. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain informed consent	X								*Continued on table below*	
Assign participant number	X									
Obtain demography and medical history data	X									
Obtain details of medications currently taken	X									
Perform physical examination	X	X	X	X	X	X	X			
Measure vital signs (including body temperature)	X	X	X	X	X	X	X			
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL				
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL									
Serological test for prior COVID-19 infection	~20 mL									
Perform urine pregnancy test (if appropriate)	X	X			X					
Obtain nasal (midturbinate) swab(s)[c]		X			X					X
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X		
Confirm eligibility	X	X			X					
Collect prohibited medication use			X	X	X	X	X	X		X

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Review hematology and chemistry results		X		X	X	X	X		*Continued on table below*	
Review temporary delay criteria		X			X					
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X		
Obtain randomization number and study intervention allocation		X								
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[d] ~170 mL	~50 mL + optional[d] ~170 mL	~50 mL + optional[d] ~170 mL		
Administer study intervention		X			X					
Assess acute reactions for at least 30 minutes after study intervention administration[e]		X			X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X								
Provide thermometer and measuring device		X			X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►	◄	———	►			

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X		*Continued on table below*	
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X		X
Collect e-diary or assist the participant to delete application										
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)										X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to potential COVID-19 illness onset.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.
e. The first 5 participants in in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	8	8a	8b	8c	9	10	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**		
Obtain informed consent		X					
Confirm participant originally received 10 to 30 µg of BNT162b1 or BNT162b2		X					
Perform urine pregnancy test (if appropriate)		X					
Confirm use of contraceptives (if appropriate)		X	X	X			
Collect prohibited medication use	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X			
Measure body temperature		X					
Confirm eligibility		X					
Review temporary delay criteria		X					
Collect blood sample for immunogenicity assessment	~20 mL	~20 mL	~20 mL	~20 mL	~20 mL		
Obtain nasal (midturbinate) swab(s)		X					X
Obtain the participant's vaccine vial allocation using the IRT system		X					
Administer 30-µg dose of BNT162b2		X					

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and extensions or variations thereof
ema.europa.eu

Visit Number	8	8a	8b	8c	9	10	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**		
Assess acute reactions for at least 30 minutes after study intervention administration		X					
Provide thermometer and measuring device		X					
Remind participant of e-diary technologies		X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		←	→				
Review ongoing reactogenicity e-diary symptoms and obtain stop dates				X			
Collect AEs and SAEs as appropriate	X	X	X	X	X[c]		X
Collect e-diary or assist the participant to delete application						X[d]	

This document cannot be used to support any marketing authorisation application and extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Visit Number	8	8a	8b	8c	9	10	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: IRT = interactive response technology; vax = vaccination.

a. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.
b. The COVID-19 illness visit may be conducted as an in-person or telehealth visit. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to potential COVID-19 illness onset.
c. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).
d. If protocol amendment 20 is approved and participants are informed of early study completion, e-diary device return should be arranged by the site.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and extensions or variations thereof
ema.europa.eu

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit is required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C. Prior to protocol amendment 16, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b2 or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b2 will continue in the study as originally planned.

All other participants who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4). If they want to receive BNT162b2, they will be unblinded and those who did originally receive placebo will move to the SoA in Section 1.3.3 for their remaining visits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[c]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Obtain informed consent	X						
Assign participant number	X						
Obtain demography and medical history data	X						
Perform clinical assessment[d]	X						
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X	
Measure height and weight	X						
Measure temperature (body)	X	X					
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X	X				
Collect nonstudy vaccine information	X	X	X	X			
Collect prohibited medication use		X	X	X	X	X	X
Confirm eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment[e]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	
Obtain nasal (midturbinate) swab	X	X					X
Obtain randomization number and study intervention allocation	X						

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[c]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Administer study intervention	X	X					
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X						
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[f]	◄►	◄►					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[f]		X	X				
Collect AEs and SAEs as appropriate	X	X	X	X[g]	X[g]	X[g]	X
According to eligibility, ascertain willingness to receive BNT162b2 if originally received placebo; if willing, unblind the participant's study intervention assignment (if not already done), and move placebo recipients to the SoA in Section 1.3.3			X ◄►	X			

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[c]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Collect e-diary or assist the participant to delete application						X[h]	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.
b. The COVID-19 illness visit may be conducted as an in-person or telehealth visit. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to potential COVID-19 illness onset.
c. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
d. Including, if indicated, a physical examination.
e. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
f. Reactogenicity subset participants only.
g. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).
h. If protocol amendment 20 is approved and participants are informed of early study completion, e-diary device return should be arranged by the site.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. Any placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2.

Visit Number	101	102	103	104	105	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**From Recommendation[c] or At Least 175 Days After Vaccination 2[d]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Confirm participant meets local/national recommending criteria or is at least 175 days after Vaccination 2 (Visit 4/Visit 2)	X					
Obtain informed consent	X					
Confirm participant originally received placebo	X					
Perform urine pregnancy test (if appropriate)	X	X				
Confirm use of contraceptives (if appropriate)	X	X				
Collect prohibited medication use	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	
Review and consider eligibility	X	X				
Review temporary delay criteria	X	X				
Collect blood sample for immunogenicity assessment[e]	~20 mL					
Obtain nasal (midturbinate) swab	X	X				X
Obtain vaccine vial allocation via IRT	X	X				
Administer BNT162b2	X	X				
Assess acute reactions for at least 30 minutes after study intervention administration	X	X				

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu

Visit Number	101	102	103	104	105	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**From Recommendation[c] or At Least 175 Days After Vaccination 2[d]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Collect AEs and SAEs as appropriate	X	X	X	X		X[f]
Contact the participant by telephone			X	X	X	
Request the participant return the e-diary or assist the participant to delete the application					X[g]	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)						X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

a. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.
b. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to potential COVID-19 illness onset.
c. For participants who become eligible according to recommendations detailed separately and available in the electronic study reference portal.
d. For any remaining Phase 2/3 placebo recipients who wish to receive BNT162b2; may be combined with Visit 4 for Phase 2/3 participants.
e. Only if the participant has no blood sample collected in the previous 7 days.
f. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).
g. If protocol amendment 20 is approved and participants are informed of early study completion, e-diary device return should be arranged by the site.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.4. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) (Subset for Evaluation of Boostability and Protection Against Emerging VOCs)

Select participants in Phase 3 at select sites who originally received 2 doses of BNT162b2 will be offered the opportunity to receive a third (and potentially fourth) dose of BNT162b2 or BNT162b2$_{SA}$.

Visit Number	301	302	303	304	305	306	307	Unplanned
Visit Description	Vax 3[a]	1-Week Follow-up Visit (After Vax 3)	1-Month Follow-up Visit (After Vax 3)	1-Week Follow-up Visit (After Vax 4)[b]	1-Month Follow-up Visit (After Vax 4)[b]	6-Month Follow-up Visit	18-Month Follow-up Visit[c]	Potential COVID-19 Illness Visit[d]
Visit Window (Days)	150 to 210 Days After Visit 2	6 to 8 Days After Visit 301	28 to 35 Days After Visit 301	6 to 8 Days After Visit 303	28 to 35 Days After Visit 303	175 to 189 Days After Visit 301	532 to 560 Days After Visit 301	Optimally Within 3 Days After Potential COVID-19 Illness Onset
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4				
Obtain informed consent	X							
Confirm participant originally received BNT162b2 at Dose 1 and Dose 2	X							
Perform urine pregnancy test (if appropriate)	X		X[b]					
Confirm use of contraceptives (if appropriate)	X	X	X	X	X			
Collect prohibited medication use	X	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X	X	X		
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X			X	X	
Measure body temperature	X		X[b]					
Confirm eligibility	X		X[b]					
Review temporary delay criteria	X		X[b]					

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Visit Number	301	302	303	304	305	306	307	Unplanned
Visit Description	**Vax 3[a]**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**1-Week Follow-up Visit (After Vax 4)[b]**	**1-Month Follow-up Visit (After Vax 4)[b]**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit[c]**	**Potential COVID-19 Illness Visit[d]**
Visit Window (Days)	**150 to 210 Days After Visit 2**	**6 to 8 Days After Visit 301**	**28 to 35 Days After Visit 301**	**6 to 8 Days After Visit 303**	**28 to 35 Days After Visit 303**	**175 to 189 Days After Visit 301**	**532 to 560 Days After Visit 301**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			**ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4**				
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation[e]	~120 mL	~120 mL	~120 mL			~120 mL		
Collect blood sample for HLA typing[e]	~5 mL							
Obtain nasal (midturbinate) swab(s)	X		X[b]					X
Obtain randomization number and study intervention allocation using the IRT system	X							
Administer study intervention	X		X[b]					
Assess acute reactions for at least 30 minutes after study intervention administration	X		X[b]					
Provide thermometer and measuring device	X							
Remind participant of e-diary technologies	X		X[b]					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	←	→		↔				
Review ongoing reactogenicity e-diary symptoms and obtain stop dates			X		X			

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	301	302	303	304	305	306	307	Unplanned
Visit Description	**Vax 3[a]**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**1-Week Follow-up Visit (After Vax 4)[b]**	**1-Month Follow-up Visit (After Vax 4)[b]**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit[c]**	**Potential COVID-19 Illness Visit[d]**
Visit Window (Days)	**150 to 210 Days After Visit 2**	**6 to 8 Days After Visit 301**	**28 to 35 Days After Visit 301**	**6 to 8 Days After Visit 303**	**28 to 35 Days After Visit 303**	**175 to 189 Days After Visit 301**	**532 to 560 Days After Visit 301**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			**ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4**				
Collect AEs and SAEs as appropriate	X	X	X	X	X	X[f]	X[f]	X
Collect e-diary or assist the participant to delete application							X[g]	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)								X

Abbreviations: e-diary = electronic diary; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; vax = vaccination.

a. Visit 301 can occur on the same day as Visit 4, but all procedures for both visits must be conducted (including collection of all blood samples).
b. Only for those participants who will receive Dose 4.
c. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.
d. The COVID-19 illness visit may be conducted as an in-person or telehealth visit. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to potential COVID-19 illness onset.
e. Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants who will receive a third (but not fourth) dose of BNT162b2 at 30 µg or $BNT162b2_{SA}$ at select sites only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).
g. If protocol amendment 20 is approved and participants are informed of early study completion, e-diary device return should be arranged by the site.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.5. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants

As part of Amendment 14, an additional cohort of BNT162b2-naïve participants will be enrolled to receive BNT162b2$_{SA}$ per the following SoA.

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[c]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain informed consent	X						
Assign participant number	X						
Obtain demography and medical history data	X						
Perform clinical assessment[d]	X						
Measure height and weight	X						
Measure temperature (body)	X	X					
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X	X	X			
Collect nonstudy vaccine information	X	X	X	X	X		
Collect prohibited medication use		X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X			X	X	X	
Confirm eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment	~50 mL		~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation[e]	~120 mL		~120 mL	~120 mL	~120 mL		
Collect blood sample for HLA typing[e]	~5 mL						
Obtain nasal (midturbinate) swab	X	X					X

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[c]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain the participant's vaccine vial allocation using the IRT system	X	X					
Administer BNT162b2$_{SA}$	X	X					
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X						
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	◄—►	◄—►					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X		X			
Collect AEs and SAEs as appropriate	X	X	X	X	X[f]	X[f]	X
Collect e-diary or assist the participant to delete application						X[g]	

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[c]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: e-diary = electronic diary; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; vax = vaccination.

a. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.
b. The COVID-19 illness visit may be conducted as an in-person or telehealth visit. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to potential COVID-19 illness onset.
c. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
d. Including, if indicated, a physical examination.
e. Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants at select sites only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).
g. If protocol amendment 20 is approved and participants are informed of early study completion, e-diary device return should be arranged by the site.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

1.3.6. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4 or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

Visit Number	201	202 Onward
Visit Description	**Asymptomatic SARS-CoV-2 Infection Surveillance Consent**	**Asymptomatic SARS-CoV-2 Infection Surveillance Swab**
Visit Window (Days)	**From Approval of Protocol Amendment 11**	**Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection**
Obtain informed consent for asymptomatic SARS-CoV-2 infection surveillance	X	
Collect prohibited medication use	X	
Collect blood sample for immunogenicity assessment[a]	~20 mL/~10 mL	
Obtain nasal (midturbinate) swab (self-swab at home or by site staff at an in-person visit)	X	X
Collect AEs and SAEs as appropriate[b]	X	

a. Only if the participant has no blood sample collected in the previous 7 days. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
b. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

1.3.7. Administration of a Third Dose of BNT162b2 to Participants Who Have Not Previously Received a Third Dose

As part of protocol amendment 18, to reflect current and anticipated recommendations for COVID-19 vaccine boosters, participants in C4591001 who have not already received one, will be offered a third dose of BNT162b2 from at least 3 months (84 days) after their second dose of BNT162. The opportunity to receive a third dose of BNT162b2 will be offered as part of the study, according to recommendations detailed separately, and available in the electronic study reference portal. This opportunity is only for those participants who received their first 2 doses of BNT162 (including BNT162b1, BNT162b2, or BNT162b2$_{SA}$) as part of the study.

Once a participant receives a vaccination at Visit 501, all remaining study visits will follow the SoA as set out below.

The additional information collected at Visits 501, 502, 503, and 504 will be collected in a supplementary database; further information on the recording of this information will be provided in the study CRF Completion Requirements document.

Visit Number	501	502	503	504	Unplanned
Visit Description	**Third Dose of BNT162b2**	**1-Month Telephone Contact**	**6-Month Telephone Contact[a]**	**12-Month Follow-up Visit[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Per Recommendation[c]**	**28 to 35 Days After Visit 501**	**175 to 189 Days After Visit 501**	**350 to 378 Days After Visit 501**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset[c]**
Confirm participant has only received 2 doses of BNT162 as part of the study and not outside the study	X				
Obtain informed consent	X				
Perform urine pregnancy test (if appropriate)	X				
Confirm use of contraceptives (if appropriate)	X				
Collect nonstudy vaccine information[d]	X	X	X		
Collect prohibited medication use[d]	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X	X	X	X	
Review and consider eligibility	X				
Review temporary delay criteria	X				
Collect blood sample for immunogenicity assessment	~20 mL			~20 mL	
Obtain nasal (midturbinate) swab	X				X
Obtain vaccine vial allocation via IRT	X				

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	501	502	503	504	Unplanned
Visit Description	**Third Dose of BNT162b2**	**1-Month Telephone Contact**	**6-Month Telephone Contact[a]**	**12-Month Follow-up Visit[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Per Recommendation[c]**	**28 to 35 Days After Visit 501**	**175 to 189 Days After Visit 501**	**350 to 378 Days After Visit 501**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset[c]**
Administer BNT162b2	X				
Assess acute reactions for at least 30 minutes after study intervention administration	X				
Collect AEs and SAEs as appropriate[d]	X	X	X		X[e]
Contact the participant by telephone		X	X		
Request the participant return the e-diary device or assist the participant to delete the application				X[f]	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)					X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

a. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.
b. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to potential COVID-19 illness onset.
c. The opportunity to receive a third dose of BNT162b2 will be offered as part of the study, according to recommendations detailed separately, and available in the electronic study reference portal.
d. AEs, nonstudy prohibited medications, and information relating to a potential COVID-19 illness will still be recorded in the original study database (see Section 8.3.1).
e. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).
f. If protocol amendment 20 is approved and participants are informed of early study completion, e-diary device return should be arranged by the site.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

1.3.8. Administration of a Fourth (or Fifth) Dose of BNT162b2 to Eligible Participants From Protocol Amendments 13, 14, and 15

As part of protocol amendment 19, eligible participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 will be offered an additional 30-µg dose of BNT162b2. BNT162-naïve participants who received 2 primary doses of 30 µg BNT162b2$_{SA}$ under protocol amendment 14 and were enrolled to receive a booster dose at Visit 501 under protocol amendment 18 are not eligible to receive an additional dose.

The additional information collected at Visits 601, 602, 603, 604, 605, and 606 will be collected in a supplementary database, and on receipt of vaccination, participants will follow the schedule as set out below; further information on the recording of this information will be provided in the study CRF Completion Requirements document.

Visit Number	601	602	603	604	605	606	Unplanned
Visit Description	**Dose 4[a]**	**1-Month Telephone Contact**	**6-Month Telephone Contact[b]**	**Dose 5[a]**	**1-Month Telephone Contact**	**6-Month Telephone Contact[b]**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**At Least 175 Days After Visit 8a OR Visit 301**	**28 to 35 Days After Visit 601**	**175 to 189 Days After Visit 601**	**At Least 175 Days After Visit 303**	**28 to 35 Days After Visit 604**	**175 to 189 Days After Visit 604**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ADDITIONAL DOSE ONLY FOR THOSE PARTICIPANTS WHO RECEIVED DOSE 3 AT VISIT 8a or VISIT 301; Participants who decline to receive a fourth dose of BNT162b2 will continue to follow schedule of assessments per Section 1.3.1 or 1.3.4 as appropriate.			**ADDITIONAL DOSE ONLY FOR THOSE PARTICIPANTS WHO RECEIVED DOSE 4 at VISIT 303; Participants who decline to receive a fifth dose of BNT162b2 will continue to follow schedule of assessments per Section 1.3.4.**			
Confirm participant has received at least 3 (or 4) prior doses as part of study and not outside and is eligible to receive fourth (or fifth) dose of BNT162b2	X			X			
Obtain informed consent	X			X			
Perform urine pregnancy test (if appropriate)	X			X			

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	601	602	603	604	605	606	Unplanned
Visit Description	**Dose 4[a]**	**1-Month Telephone Contact**	**6-Month Telephone Contact[b]**	**Dose 5[a]**	**1-Month Telephone Contact**	**6-Month Telephone Contact[b]**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**At Least 175 Days After Visit 8a OR Visit 301**	**28 to 35 Days After Visit 601**	**175 to 189 Days After Visit 601**	**At Least 175 Days After Visit 303**	**28 to 35 Days After Visit 604**	**175 to 189 Days After Visit 604**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ADDITIONAL DOSE ONLY FOR THOSE PARTICIPANTS WHO RECEIVED DOSE 3 AT VISIT 8a or VISIT 301; Participants who decline to receive a fourth dose of BNT162b2 will continue to follow schedule of assessments per Section 1.3.1 or 1.3.4 as appropriate.			**ADDITIONAL DOSE ONLY FOR THOSE PARTICIPANTS WHO RECEIVED DOSE 4 at VISIT 303; Participants who decline to receive a fifth dose of BNT162b2 will continue to follow schedule of assessments per Section 1.3.4.**			
Confirm use of contraceptives (if appropriate)	X			X			
Collect nonstudy vaccine information[d]	X	X		X	X		
Collect prohibited medication use[d]	X	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load[e]	X	X	X	X	X	X	
Review and consider eligibility	X			X			
Review temporary delay criteria	X			X			
Obtain nasal (midturbinate) swab	X			X			X
Obtain vaccine vial allocation via IRT	X			X			
Administer BNT162b2	X			X			
Assess acute reactions for at least 30 minutes after study intervention administration	X			X			
Collect AEs and SAEs as appropriate[d]	X	X		X	X		X[f]
Contact the participant by telephone		X	X		X	X	
Request the participant return the e-diary device or assist the participant to delete the application			X		X	X[g]	

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	601	602	603	604	605	606	Unplanned
Visit Description	**Dose 4[a]**	**1-Month Telephone Contact**	**6-Month Telephone Contact[b]**	**Dose 5[a]**	**1-Month Telephone Contact**	**6-Month Telephone Contact[b]**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**At Least 175 Days After Visit 8a OR Visit 301**	**28 to 35 Days After Visit 601**	**175 to 189 Days After Visit 601**	**At Least 175 Days After Visit 303**	**28 to 35 Days After Visit 604**	**175 to 189 Days After Visit 604**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ADDITIONAL DOSE ONLY FOR THOSE PARTICIPANTS WHO RECEIVED DOSE 3 AT VISIT 8a or VISIT 301; Participants who decline to receive a fourth dose of BNT162b2 will continue to follow schedule of assessments per Section 1.3.1 or 1.3.4 as appropriate.			**ADDITIONAL DOSE ONLY FOR THOSE PARTICIPANTS WHO RECEIVED DOSE 4 at VISIT 303; Participants who decline to receive a fifth dose of BNT162b2 will continue to follow schedule of assessments per Section 1.3.4.**			
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology; vax = vaccination.

a. Applicable to those eligible participants per protocol amendments 13, 14, and 15 who received Dose 3 at Visit 8a or 301 or Dose 4 at Visit 303.
b. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.
c. The COVID-19 illness visit may be conducted as an in-person or telehealth visit. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to potential COVID-19 illness onset.
d. AEs and SAEs, nonstudy vaccines and prohibited medications, and information relating to a potential COVID-19 illness will still be recorded in the original study database.
e. Not required to be recorded for Phase 1 participants who received Dose 3 at Visit 8a.
f. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).
g. If protocol amendment 20 is approved and participants are informed of early study completion, e-diary device return should be arranged by the site.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. As of 27 February 2022, over 433 million confirmed cases and over 5.9 million deaths have been reported globally, demonstrating an urgent need for efficacious vaccines.[3]

Numerous COVID-19 vaccines are currently in development globally, and several candidate COVID-19 vaccines (eg, mRNA vaccines and adenovirus-vectored vaccines expressing the S protein) have been shown to be efficacious in the prevention of COVID-19 in clinical studies and are now available under temporary or emergency authorizations. BNT162b2, an RNA-based COVID-19 vaccine given as a 2-dose series administered 21 days apart, was shown to be safe and effective in a Phase 1/2/3 study and has received authorizations for temporary or emergency use or marketing authorizations in multiple countries and has been fully licensed for use in individuals 16 years of age and above in the US as of 23 Aug 2021.

As more data about COVID-19 continue to accrue, the potential duration of protection afforded after a wild-type SARS-CoV-2 infection, and by vaccination, remains unknown. In addition, mutated SARS-CoV-2 VOCs have started to emerge, for example in the UK

(known as 20I/501Y.V1, VOC 202012/01, or B.1.1.7), SA (known as 20H/501Y.V2 or B.1.351), and Brazil (known as P.1).[4]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[5,6]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Three SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 3 antigens:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5);
- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9);
- **BNT162b2s01** (variant RBP020.11): nucleoside-modified messenger RNA (modRNA) as above, but encoding the P2 S containing South Africa B.1.351 variant–specific mutations, hereafter referred to as BNT162b2$_{SA}$, as a representative variant of concern (VOC).

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

In light of the unknowns regarding duration of protection, as well as the emerging VOCs, it is important to understand the boostability of BNT162, and potential heterologous protection against emerging VOC(s). A first step to address this will be to study an additional dose of BNT162b2 at 30 µg given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ (based upon the South African variant and hereafter referred to as

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof are not proposed.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

BNT162b2$_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

As part of protocol amendment 18, to reflect current and anticipated recommendations for COVID-19 vaccine boosters, participants in C4591001 who meet specified recommendations and have not already received one, will be offered a third dose of BNT162b2 after their second dose of BNT162b1, BNT162b2 or BNT162b2$_{SA}$. The opportunity to receive a third dose of BNT162b2 will be offered as part of the study, according to recommendations detailed separately, and available in the electronic study reference portal.

As part of protocol amendment 19, Phase 1/2/3 participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 will be offered an additional dose of BNT162b2 at 30 µg at least 6 months after their last dose of BNT162b2 (or BNT162b2$_{SA}$).

Since the initiation of this study, many protocol amendments have been implemented in order to adapt to expanding knowledge about COVID-19, the emergence of VOCs, and growing knowledge about duration of vaccine effectiveness. These amendments have included unblinding and vaccination of initial placebo recipients and administration of booster doses, to ensure that participants have been protected in line with national and local guidelines as they have been determined. Therefore, the study is now fully unblinded with no control arm, making it observational in nature and the active safety surveillance period for the majority of participants has completed. Real-world studies of both safety and effectiveness of BNT162b2 have contributed enormously, and continue to do so, to the knowledge about the vaccine beyond what is possible within the clinical trial setting. In view of this, and with agreement of the FDA and EMA, protocol amendment 20 will truncate participants' study involvement to allow early completion of the study without the need to complete all study visits as per the SoA. Following the appropriate approvals of protocol amendment 20, participants will be informed via the study sites that their participation in the study will be concluded with no further data collection required from that point onwards.

Protocol amendment 20 will also remove the objective to describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." As of 03 July 2022, more than 3.6 billion doses of BNT162b2 have been distributed,[7] with over 1.4 billion doses of BNT162b2 administered worldwide,[8] which were manufactured via "Process 2." Given the number of doses now administered globally, the originally planned manufacturing process comparison is no longer warranted.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

2.3. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[9] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[10] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.4. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with the currently available therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.

- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.

- All participants 12 to 15 years of age will be included in the reactogenicity subset (see Section 8.2.2).

This document cannot be used to support a marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

2.4.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[11]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.
Very rare cases of anaphylaxis, myocarditis, and pericarditis have been reported after authorization in recipients of BNT162b2.	Anaphylaxis: Frequency not known. Myocarditis and pericarditis: Very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. These are generally mild cases, and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.	Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 8.22.

2.4.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of an efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.4.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1 and 6 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults at least 6 months after the second dose of either BNT162b1 or BNT162b2	• GMCs/GMTs at the time of Dose 3, 7 days and 1 month after Dose 3, and 12 months after Dose 2 • GMFRs from before Dose 3 to 7 days and 1 month after Dose 3 and 12 months after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels
	• GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers
	• GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers
To describe the safety profile of third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2 given as a fourth dose at least 6 months after the third dose of BNT162b2 for participants who received a fourth dose as part of protocol amendment 19	In participants receiving a fourth dose of study intervention, the percentage of participants reporting: • AEs and SAEs from Dose 4 to 1 month after Dose 4	• AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any enlargements or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
To describe the safety and tolerability profile of BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants, or as 2 doses to BNT162b2-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 5 or 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2 given as a third dose at least 3 months after the second dose of BNT162b2 (or BNT162b2$_{SA}$) for participants who received a third dose as part of protocol amendment 18	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • AEs and SAEs from Dose 3 to 1 month after Dose 3	• AEs • SAEs
To describe the safety and tolerability profile of BNT162b2 given as a fourth (or fifth) dose at least 6 months after the third (or fourth) dose of BNT162b2 (or BNT162b2$_{SA}$) for participants who received a fourth (or fifth) dose as part of protocol amendment 19	In participants receiving a fourth (or fifth) dose of study intervention, the percentage of participants reporting: • AEs and SAEs from Dose 4 (or Dose 5) to 1 month after Dose 4 (or Dose 5)	• AEs • SAEs
Primary Immunogenicity ***BNT162b2-experienced participants***		
To demonstrate the noninferiority of the anti–reference strain immune response after a third dose of BNT162b2 at 30 µg compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Objectives[a]	Estimands	Endpoints
BNT162b2-naïve participants		
To demonstrate the noninferiority of the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
BNT162b2-experienced participants		
To demonstrate the noninferiority of the anti-SA immune response after a third dose of BNT162b2 at 30 µg compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti–reference strain immune response after 1 dose of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation applications or any extensions or variations thereof
www.ema.europa.eu

Objectives[a]	Estimands	Endpoints
To descriptively compare the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ and a third dose of BNT162b2 at 30 µg	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg	SARS-CoV-2 SA NT in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$ or the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ and the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate a statistically greater anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 SA NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
To descriptively compare the anti–reference strain immune response after 2 doses of BNT162b2$_{SA}$ and after 2 doses of BNT162b2	GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants after receipt of each dose of BNT162b2: Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT at baseline and 1 and 6 months after Dose 2 and GMFR from baseline to 1 and 6 months after Dose 2	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate and characterize the SARS-CoV-2 isolate in cases of: • Confirmed COVID-19 cases that occur through approximately 6 months after the second dose • Confirmed severe COVID-19 cases that occur through approximately 6 months after the second dose		• SARS-CoV-2 neutralizing titers • Identification of SARS-CoV-2 variant(s)
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the immune response to any VOCs not already specified	Geometric mean NT for any VOCs not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2	• SARS-CoV-2 NTs for any VOCs not already specified
To describe the immune response to a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$	• GMTs at Dose 3 and subsequent time points • GMFRs from Dose 3 to subsequent time points	• SARS-CoV-2 reference strain NTs
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and SA in a subset of participants: • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 2 doses to BNT162b2-naïve participants • 7 Days and 1 and 6 months after BNT162b2 given as a third dose to BNT162b2-experienced participants		

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Up until the final efficacy analysis, this protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ at 30 µg (based upon the South African variant and hereafter referred to as BNT162b2$_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

As part of protocol amendment 19, eligible participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 will be offered an additional 30-µg dose of BNT162b2. BNT162-naïve participants who received 2 primary doses of 30 µg BNT162b2$_{SA}$ under protocol amendment 14 and were enrolled to receive a booster dose at Visit 501 under protocol amendment 18 are not eligible to receive an additional dose.

Protocol amendment 20 will truncate participants' study involvement to allow early completion of the study without the need to complete all study visits as per the SoA.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc europaeed

- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
    - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
    - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than at the approximate time participants in Phase 2/3 reach Visit 4.

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This group of participants will also be offered a fourth dose of BNT162b2 at 30 µg at least 6 months after their third dose.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

approximately 6 to 12 months after their second dose of BNT162. A further fourth dose of BNT162b2 at 30 µg will be offered to these participants at least 6 months after their third dose.

Participants are expected to participate for up to a maximum of approximately 26 months.

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 280 participants from each of the 2 age groups (12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. Protocol amendment 20 removes the objective to describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"; considering the number of doses of BNT162b2 distributed and administered globally, this comparison is no longer warranted.

For evaluation of boostability and protection against emerging VOCs, 600 existing Phase 3 participants 18 to 55 years of age will be rerandomized in a 1:1 ratio to receive either a third dose of BNT162b2 at 30 µg or a third dose of BNT162b2$_{SA}$.

A further group of approximately 144 existing Phase 3 participants 18 years of age and older will be enrolled to receive a third, lower, dose of BNT162b2 of either 5 or 10 µg. Approximately 24 participants 18 to 55 years of age and 48 participants >55 years of age will be enrolled in each dose group. An additional group of 30 existing Phase 3 participants 18 to 55 years of age will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$. For these 30 participants, through 1 month after their first dose of BNT162b2$_{SA}$ the participant will be blinded to their vaccine allocation but the investigator and Sponsor will not be. Serum samples from these participants may be used for assay development purposes and, except for objectives relating to response to a fourth dose, their results will be analyzed separately from the main immunogenicity analyses.

Three hundred participants 18 to 55 years of age who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19 will be enrolled as a new cohort of participants to receive BNT162b2$_{SA}$ given as a 2-dose series.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 2/3 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4).

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

The changes to the protocol as part of protocol amendment 14 to assess boostability and homologous/heterologous protection against emerging VOCs allow the evaluation of safety and immunogenicity of BNT162b2$_{SA}$:

- When given as a third dose to C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously (ie, BNT162b2-experienced) and have not experienced COVID-19.

- In a small separate group of individuals who previously received 2 doses of BNT162b2 followed by 1 dose of BNT162b2$_{SA}$, a second BNT162b2$_{SA}$ dose will also be given 1 month after Dose 1 of BNT162b2$_{SA}$.

- When given as a 2-dose series, separated by 21 days, in newly recruited participants who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19.

In addition, a group of C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously will receive a third dose of BNT162b2.

This approach will allow an evaluation of immunogenicity against the reference ancestral SARS-CoV-2 strain (Wuhan-Hu-1/USA-WA1) and the selected South African VOC, using a noninferiority approach based on neutralizing antibody titers in prior BNT162b2 vaccinees who receive either a homologous boost (with BNT162b2) or a heterologous boost (with BNT162b2$_{SA}$), as well as new vaccinees receiving 2 doses of BNT162b2$_{SA}$.

As part of protocol amendment 18, to reflect current and anticipated recommendations for COVID-19 vaccine boosters, participants in C4591001 who meet specified recommendations (detailed separately and available in the electronic study portal) and have not already received one, will be offered a third dose of BNT162b2 after their second dose of BNT162. The opportunity to receive a third dose of BNT162b2 will be offered as part of the study, according to recommendations detailed separately, and available in the electronic study reference portal. This opportunity is only for those participants who received their first 2 doses of BNT162 (including BNT162b1, BNT162b2, or BNT162b2$_{SA}$) as part of the study.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.6. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

As part of protocol amendment 19, eligible participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 will be offered an additional 30-µg dose of BNT162b2. BNT162-naïve participants who received 2 primary doses of 30 µg BNT162b2$_{SA}$ under protocol amendment 14 and were enrolled to receive a booster dose at Visit 501 under protocol amendment 18 are not eligible to receive an additional dose.

To provide maximum opportunity for all participants to receive the third dose of BNT162b2 under protocol amendment 18, protocol amendment 19 reduces the eligibility window from at least 6 months after Dose 2 to at least 3 months after Dose 2.

As part of protocol amendment 19, the study may be terminated early for reasons including but not limited to the increased access and availability of BNT162b2 in the real world, reducing the value of participant involvement and observation in this clinical trial.

Further to this, participants who are offered the possibility to participate in a future study within the Pfizer/BioNTech COVID-19 vaccine development program will be discontinued from this study.

Following the appropriate approvals of protocol amendment 20, participants will be informed via the study sites that their participation in the study will be concluded with no further data collection required from that point onwards, and there will be no requirement to complete any outstanding study visits or procedures.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness visit will occur and, prior to protocol amendment 16, a

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

subsequent convalescent visit would occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

This document cannot be used to support and marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

Following the appropriate approvals of protocol amendment 20, participants will be informed via the study sites that their participation in the study will be concluded with no further data collection required from that point onwards. Therefore, as of protocol amendment 20, all active participants are considered to have reached the end of the study, without the need to complete any outstanding study visits or procedures as per the relevant SoA. Section 8 outlines the activities that should be performed after approval of protocol amendment 20.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization.

   For the boostability and protection-against-VOCs subset:

   - Existing participants enrolled to receive a third dose of BNT162b2 at 30 µg or BNT162b2$_{SA}$; male or female participants between the ages of 18 and 55 years, inclusive, at rerandomization.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Newly enrolled participants enrolled to receive 2 doses of BNT162b2$_{SA}$; male or female participants between the ages of 18 and 55 years, inclusive, at enrollment.
- Existing participants enrolled to receive a third dose of BNT162b2 at 5 or 10 µg; male or female participants ≥18 years at rerandomization.

- Note that participants <18 years of age cannot be enrolled in the EU.
- Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

5. **Boostability and protection-against-VOCs existing participant subset only:** Participants who provided a serum sample at Visit 3, with Visit 3 occurring within the protocol-specified window.

Informed Consent:

6. Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - Chronic liver disease
    - Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
    - Resident in a long-term facility
    - BMI >30 kg/m^2
    - Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry through and including 28 days after the last dose of study intervention, with the exception of non-Pfizer interventional studies for prevention of COVID-19, which are prohibited throughout study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
   - New or increased cough;
   - New or increased shortness of breath;
   - Chills;
   - New or increased muscle pain;
   - New loss of taste/smell;
   - Sore throat;
   - Diarrhea;
   - Vomiting.
2. Receipt of any seasonal or pandemic influenza vaccine within 14 days (not applicable for the third, fourth, or fifth dose of BNT162b2 at Visits 501, 601, or 604, respectively), or any other nonstudy vaccine within 28 days, before study intervention administration.
3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days (not applicable for the third, fourth, or fifth dose of BNT162b2 at Visits 501, 601, or 604, respectively, or any other nonstudy vaccine within 28 days, after study intervention administration.
4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 3 investigational RNA vaccine candidates, with the addition of saline placebo, are the 4 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 5 µg, 10 µg, 20 µg, 30 µg
- BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S containing South Africa B.1.351 variant–specific mutations): 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	5-, 10-, 20-, 30-µg	30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

Protocol amendment 20 will also remove the objective to describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." As of 03 July 2022, more than 3.6 billion doses of BNT162b2 have been distributed, with over 620 million doses of BNT162b2 administered worldwide, which were manufactured via "Process 2." Given the number of doses now administered globally, the originally planned manufacturing process comparison is no longer warranted.

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. Participants who originally received placebo and accept the offer to receive BNT162b2 at defined points as part of the study will receive 1 dose of BNT162b2 at each additional vaccination visit (Visits 101 and 102) in accordance with the study's additional SoA (Section 1.3.3). The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162 at Visit 8a.

Participants in the subset for evaluation of boostability and protection against emerging VOCs will receive either a third dose of BNT162b2 or BNT162b2$_{SA}$ approximately 5 to 7 months after their second dose of BNT162 at Visit 301. Of those who receive BNT162b2$_{SA}$ at Visit 301, a subset will receive a further dose of BNT162b2$_{SA}$ at Visit 303.

BNT162b2-naïve participants who are enrolled under protocol amendment 14 to receive BNT162b2$_{SA}$ will receive 1 dose of study intervention at each vaccination visit, Visits 401 and 402.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

As part of protocol amendment 18, participants who have not yet received a third dose of BNT162b2 may receive one at Visit 501, at least 3 months (84 days) after their second dose of BNT162. The administration of a third dose of BNT162b2 at Visit 501 will be conducted in an open-label manner; therefore, the requirement for an unblinded dispenser/administrator does not apply to this vaccination.

As part of protocol amendment 19, eligible participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 may receive an additional dose of 30 µg BNT162b2 at Visit 601 or 604, at least 6 months after their last dose of BNT162. The administration of a fourth (or fifth) dose of BNT162b2 at Visit 601 or 604 will be conducted in an open-label manner; therefore, the requirement for an unblinded preparer, dispenser, and administrator does not apply to this vaccination.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

9. Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded. The visits added in protocol amendment 19 (Visits 601 through 606) will be conducted in an open-label manner; therefore, the requirement for an unblinded preparer, dispenser, and administrator does not apply to this vaccination.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

To allow administration of BNT162b2 to participants who originally received placebo, site staff will be unblinded to individual participants' original study intervention allocation as the participants become eligible for vaccination under local/national recommendations or from 6 months after the second dose.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document can only be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

For the group of 30 existing Phase 3 participants 18 to 55 years of age who will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the investigator will not be.

The administration of the third and fourth (or fifth) dose of BNT162b2 at Visits 501 and 601 (or 604), respectively, will be conducted in an open-label manner.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).

- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

This document cannot be used to support ema.europa.eu marketing authorisation application and any extensions or variations thereof

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- After the formal data release of the final efficacy analysis of at least 164 cases, which is considered the primary completion of the study efficacy objectives, additional statisticians and programmers will become unblinded at the participant level to prepare unblinded analyses and other regulatory activities. A group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study.

- After the study data used for submission become public, the blinded study team will also have access to those data, and become unblinded at a group level.

- When a participant is unblinded for potential receipt of BNT162b2 (if he or she originally received placebo) per Section 8.16, the study team will become unblinded to the participant's original study intervention allocation.

For the group of 30 existing Phase 3 participants 18 to 55 years of age who will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the sponsor will not be.

The study will be unblinded in stages once all ongoing participants either have been individually unblinded or have concluded their 6-month post–Dose 2 or post–Dose 3 study visit, as follows:

- Phase 1 (after Visit 8).

- Phase 2/3, ≥16 years (after Visit 4).

- Phase 3, 12 to 15 years (after Visit 4).

- Original Phase 3 participants rerandomized to assess boostability and protection against emerging VOCs (after Visit 306).

The administration of the third and fourth (or fifth) dose of BNT162b2 at Visits 501 and 601 (or 604), respectively, will be conducted in an open-label manner.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

Instructions on how to unblind participants ahead of administration of BNT162b2 to placebo recipients, or for other, nonemergency reasons, will be provided separately: this unblinding will NOT be performed in the IRT. The date (that the participant becomes aware of study intervention allocation) and reason that the blind was broken must be recorded in the source documentation and CRF.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants). In addition, for Phase 1 participants who go on to receive a third dose of BNT162, concomitant vaccinations will be collected from the time the participant provides informed consent (for receipt of vaccination 3) through and including Visit 8c (1 month after the third dose). For BNT162-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to the time the participant provides informed consent (for participation in the subset) through and including Visit 306. For BNT162b2-naïve participants, the subset for evaluation of protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to study enrollment through and including Visit 405. For participants who receive a third dose of BNT162b2 at Visit 501, all vaccinations received will be recorded from 28 days prior to the time the participant provides informed consent (for receipt of the third dose) through Visit 503. For participants who receive a fourth (or fifth) dose of BNT162b2 at Visit 601 or 604 all vaccinations received will be recorded from 28 days prior to the time the participant provides informed consent for receipt of the fourth (or fifth) dose through 1 month after vaccination (Visit 602 or 605.
- Nonstudy coronavirus vaccines are listed in Section 6.5.1 as prohibited throughout the study and should therefore be recorded at any time they are given during study participation. This includes blinded BNT162b2 vaccine/placebo given in the B7471026 study.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention. For participants receiving the third dose of BNT162b2 at Visit 501, or the fourth (or fifth) dose of BNT162b2 at Visit 601 (or 604), the administration of the seasonal and pandemic influenza vaccine is not prohibited.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 and from 28 days prior to Visit 8a to Visit 8c for Phase 1 participants, and from 28 days prior to enrollment to Visit 3 for Phase 2/3 participants). Use is also prohibited for participants in the subset for evaluation of boostability and protection against emerging VOCs, from 28 days prior to Visit 301 to Visit 303/305 and the BNT162b2-naïve participants from 28 days prior to enrollment to Visit 404.

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, for whatever reason, a participant receives only 1 dose of BNT162b2, the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. This opportunity also extends to the third, fourth, and fifth doses of BNT162b2, in the event of an issue with the planned administration. For example, because of a medication error a participant receives only 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa); the participant can return at a later date for the unscheduled visit. In this situation:

- Obtain informed consent.
- Measure the participant's body temperature (only in the event the unscheduled visit is to administer a second, not third, fourth, or fifth dose).
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Unblinded or blinded (depending on time point in the study) site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s). Following protocol amendment 19, the mandatory follow-up period for SAE collection will be at least 1 month after the third dose for all participants enrolled under protocol amendment 18.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu

- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

Note: Participants who are randomized in the C4591031 or the BNT162-17 study should be withdrawn from this study.

From protocol amendment 18 onwards, participants who receive COVID-19 vaccines outside of the study should be withdrawn. This does not apply if the nonstudy COVID-19 vaccine was administered prior to site receipt of IRB/EC approval of protocol amendment 18.

As part of protocol amendment 19, the study may be terminated early for reasons including but not limited to the increased access and availability of BNT162b2 in the real world, reducing the value of participant involvement and observation in this clinical trial. As part of protocol amendment 20, following agreement with the FDA and EMA, all outstanding study visits for all active study participants will not be required to be completed. Once protocol amendment 20 has been approved, participants will be informed of early study completion and no further data will be collected.

Further to this, participants who are offered the possibility to participate in a future study within the Pfizer/BioNTech COVID-19 vaccine development program will be discontinued from this study.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

If a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. Following the appropriate approvals of protocol amendment 20, all active participants will be contacted by the site by telephone to inform them of the changes brought about by protocol amendment 20. At this telephone contact participants within the mandatory AE reporting period will have up-to-date AE data collected and all participants will have their final disposition CRF completed to conclude their study participation; the date of study completion in the final disposition CRF will be the date of the telephone contact. No further data will be collected after that point, and no further study visits or procedures should be completed. If participants cannot be contacted via telephone, all steps outlined in Section 7.3 should be followed to confirm the participant is lost to follow-up.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately up to: 500 mL for participants in Phase 1, 150 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 670 mL during the 24-month study period.

For those Phase 3 participants enrolled in the subset to receive an additional dose of BNT162b2 or BNT162b2$_{SA}$, the total blood sampling volume for individual participants in this study is approximately up to 310 mL for those who receive 3 doses and 410 mL for those who receive 4 doses. Those participants in the subset who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of approximately up to 795 mL.

For those participants enrolled into the additional cohort (added as part of protocol amendment 14) of BNT162b2-naïve participants who will receive 2 doses of BNT162b2$_{SA}$, the total blood sampling volume for individual participants is approximately up to 250 mL. Those participants in the cohort who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of approximately up to 735 mL.

For all participants, other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

8.1.1. Efficacy Against COVID-19

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[12] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
    - Fever;
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste or smell;
    - Sore throat;
    - Diarrhea;
    - Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction*;
- Admission to an ICU;
- Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

8.1.2. Efficacy Against Asymptomatic SARS-CoV-2 Infection

VE against asymptomatic SARS-CoV-2 infection will be evaluated in 2 ways, through impact on seroconversion of N-binding antibody and impact on NAAT-confirmed SARS-CoV-2 infection, in originally enrolled Phase 2/3 participants not suffering from COVID-19. Data from participants who receive more than 2 doses of BNT162b2 will not be included after they receive a third dose.

8.1.2.1. Seroconversion of N-Binding Antibody

Blood samples for assessment of N-binding antibodies are drawn at multiple scheduled visits. An asymptomatic case of SARS-CoV-2 infection based on seroconversion of N-binding antibody is defined as positive N-binding antibody at a post–Dose 2 visit in participants without serological evidence of infection (determined by negative N-binding antibody) at Visit 1 or virological evidence of infection (determined by negative NAAT result at Visit 1 and Visit 2, and at the time of a potential COVID-19 illness). The requirement for a negative NAAT result at Visit 2 is to focus on assessment of protection against asymptomatic infection after 2 doses of vaccine, to the extent possible in an analysis based on seroconversion of N-binding antibody, recognizing that it is not possible to identify and exclude all asymptomatic infections that occur after Dose 1 and prior to Dose 2.

A secondary definition will be applied without the requirement for a negative NAAT result at Visit 2 to allow assessment of protection after 1 dose of vaccine. A positive N-binding antibody at a postvaccination visit in participants with negative N-binding antibody at Visit 1 and negative NAAT results at Visit 1 and at the time of a potential COVID-19 illness is considered an asymptomatic case.

This document can not be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

8.1.2.2. NAAT-Confirmed SARS-CoV-2 Infection

For participants who consent to participate in an intensive period of surveillance, nasal swabs will be obtained to assess SARS-CoV-2 infection by NAAT (see Section 8.1.5).

An asymptomatic case of NAAT-confirmed SARS-CoV-2 infection is defined as a positive NAAT result on a nasal swab collected during the surveillance period from participants without COVID-19 symptoms at the time the nasal swab was taken, or within 14 days after it. The onset date of the asymptomatic case is the collection date of the first nasal swab that tested positive.

8.1.3. Vaccine-Induced Immunogenicity

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay (reference strain and SA variant)
- Full-length S-binding or S1-binding IgG level assay
- RBD-binding IgG level assay (Phase 1 only)

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

Additional whole blood samples of ~120 mL will be obtained from a group of up to approximately 30 participants in each 30-µg group in the subset for evaluation of boostability and protection against emerging VOCs (both BNT162b2-experienced and BNT162b2-naïve) at select sites for isolation of PBMCs. These samples will be used to describe T-cell responses to emerging VOCs and reference strains. Some of the sample may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs, for understanding the B-cell, T-cell, and antibody repertoires. A blood sample of ~5 mL for HLA typing will also be obtained. Some of the 5-mL blood sample collected for HLA typing may be used for DNA and/or RNA isolation to further characterize HLA type.

8.1.4. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine related assay work supporting vaccine programs. No testing of the participant's DNA will be performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

8.1.5. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.6.

The nasal swabs will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2. For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with Section 8.3.2.

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Certain participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. In addition, participants 16 through 17 years of age enrolled under protocol amendment 9 and onwards will be included in the reactogenicity subset. All other participants, including those who originally received placebo and then received BNT162b2 under protocol amendment 10 and onwards, will not complete a reactogenicity e-diary but will have their local reactions and systemic events detected and reported as AEs in accordance with Section 8.3.2. Phase 1 participants who receive a third dose of BNT162b2 will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage in the reactogenicity e-diary for 7 days following administration of the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

study intervention. Participants in the subset for evaluation of boostability and protection against emerging VOCs (both BNT162b2-experienced and BNT162b2-naïve) will be asked to monitor and record local reactions, systemic events, and antipyretic medication use in the reactogenicity e-diary for 7 days following each administration of the study intervention.

The participants receiving a third, fourth, or fifth dose of BNT162b2 at Visits 501, 601, or 604 will not complete a reactogenicity e-diary following vaccination.

The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device upon approval of protocol amendment 20.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[11]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the administration of the second dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema europa eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

Administration of BNT162b2 to pregnant participants at Visits 101 and 102 (participants who originally received placebo and choose to be unblinded and receive BNT162b2) or at Visits 501, 601, and 604 may be considered if there are local or national recommendations for COVID-19 vaccination of pregnant women, and the investigator and participant are in agreement. This overrides the requirements stated in the previous paragraph, and will not be considered as a protocol deviation. However, the EDP should still be reported in accordance with Section 8.3.5.1.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Additionally, for those participants who originally received placebo but go on to receive BNT162b2 at Vaccinations 3 and 4, AEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) through and including Visit 103. SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) to approximately 6 months after the second dose of BNT162b2 (Visit 104).

For Phase 1 participants who go on to receive a third dose of BNT162, AEs and SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccination 3) through and including Visit 8c (1 month after the third dose).

For BNT162b2-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, AEs will be collected from the time the participant provides informed consent (for participation in the subset) through and including Visit 303 for those receiving 1 additional dose and Visit 305 for those who receive 2 additional doses. For both schedules, this equates to collection for up to 1 month after the last dose. SAEs will be collected from the time the participant provides informed consent (for participation in the subset) through and including Visit 306 (5 or 6 months after the last dose, depending upon group).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

For BNT162b2-naïve participants, the subset for evaluation of protection against emerging VOCs, AEs will be collected from the time the participant provides informed consent through and including Visit 404 (1 month after the second dose). SAEs will be collected from the time the participant provides informed consent through and including Visit 405 (6 months after the second dose).

For participants who receive a third dose of BNT162b2 at Visit 501, AEs will be collected from the time the participant provides informed consent (for administration of the third dose of BNT162b2) through Visit 502 (1 month after the third dose of BNT162b2). SAEs will be collected from the time the participant provides informed consent (for administration of the third dose of BNT162b2) through Visit 503 (6 months after the third dose of BNT162b2). Under protocol amendment 19, the mandatory follow-up period for SAE collection will be at least 1 month after the third dose for all participants enrolled under protocol amendment 18.

For participants who receive a fourth (or fifth) dose of BNT162b2 at Visit 601 (or 604), AEs and SAEs will be collected from the time the participant provides informed consent (for administration of the fourth [or fifth] dose of BNT162b2) through Visit 602 (or 605) (1 month after the fourth [or fifth] dose of BNT162b2).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose of study intervention. Beyond 28 days after the last dose of study intervention, any pregnancy that occurs will not be considered EDP for this study.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case by case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.6. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.6.1. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

8.3.7. Cardiovascular and Death Events

Not applicable.

8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.9. Adverse Events of Special Interest

The following events are considered AESIs:

- A confirmed diagnosis of myocarditis or pericarditis. See Section 8.22 for additional procedures for monitoring of potential myocarditis or pericarditis.

8.3.9.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.10. Medical Device Deficiencies

Not applicable.

8.3.11. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Some of the blood samples collected for PBMC isolation and HLA typing may be used for DNA and/or RNA isolation. The DNA and/or RNA samples from the PBMC isolation may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs, for understanding the B-cell, T-cell, and antibody repertoires. The DNA and/or RNA samples from the blood sample for HLA typing may be used to further characterize HLA type.

See Appendix 9 for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

Unless stated otherwise, all study visits are intended to be conducted in person at the study site. If this is not possible, because of local circumstances related to the COVID-19 pandemic, study procedures that do not require in-person participant contact may be performed by telehealth. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Irrespective of the nature of the contact, all visit procedures are expected to be performed on the same day.

As the protocol design includes visits of an unplanned nature, multiple visits may occur on the same day, but all procedures for all visits must be conducted (including collection of all blood samples).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Following the appropriate approvals of protocol amendment 20, all active participants will be contacted by the study site by telephone to inform them of the changes brought about by protocol amendment 20. At this telephone contact participants within the mandatory AE reporting period will have up-to-date AE data collected and all participants will have their final disposition CRF completed to conclude their study participation. AEs, concomitant medications, and potential COVID-19 illnesses that are ongoing at the end of the study should be marked as ongoing. No further data will be collected after that point, and no further study visits or procedures should be completed.

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Between Visits 8 and 9

All participants who have not already been unblinded, no later than at the approximate time participants in Phase 2/3 reach Visit 4, will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, he or she will move to the procedures in Section 8.16.

8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of a third dose of BNT162, his or her next visit should be Visit 9.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Confirm that the participant originally received 10-µg, 20-µg, or 30-µg doses of BNT162b1 or BNT162b2 at Vaccinations 1 and 2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Record nonstudy vaccinations as described in Section 6.5.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 2, 3, and 6 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer a 30-µg dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
    - Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):
  - Fever ≥39.0°C (≥102.1°F)
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)
  - Severe pain at the injection site
  - Any severe systemic event
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Request the participant return the e-diary device or assist the participant to delete the application from his or her personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.

    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

    - Fever ≥39.0°C (≥102.1°F).

    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

    - Severe pain at the injection site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.

- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu/
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.

- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).

- Discuss contraceptive use as described in Section 10.4.

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- If Visit 3 is being conducted under amendment 12 onward: If the participant is eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, determine if he/she is willing to receive BNT162b2 as part of the study. If so, unblind the participant's study intervention assignment, and move placebo recipients to the procedures in Section 8.16.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- If not already unblinded, unblind the participant's study intervention assignment, and move placebo recipients willing to receive BNT162b2 to the procedures in Section 8.16.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).
- Request the participant return the e-diary device or assist the participant to delete the application from his or her personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination (either as part of this study, co-enrolled C459 studies, or the B7471026 [20vPnC] study), potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

their usual provider. Sites must arrange return of the participant's e-diary or assist the participant to remove the study application from his or her own personal device at the time of final telephone contact after approval of protocol amendment 20.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to potential COVID-19 illness onset. Any illness visits not concluded by the time of study completion should be considered ongoing and no further data should be collected.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.

- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:

  - Symptoms and signs, including

    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)

    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)

    - Significant acute renal, hepatic, or neurologic dysfunction

    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

  - Clinical diagnosis

  - Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.

  - Full blood count

  - Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein

  - Imaging results (eg, CT or MRI scan) to document neurologic dysfunction

  - Number and type of any healthcare contact; duration of hospitalization and ICU stay

  - Death

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

Prior to protocol amendment 16, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol; however, data collected from convalescent visits that occurred prior to protocol amendment 16 will remain part of the study data set.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

8.15. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 or 14 days after receipt of the second dose, depending on the objective) of past SARS-CoV-2 infection.

- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

- Asymptomatic SARS-CoV-2 infection surveillance visits: To determine the incidence of asymptomatic SARS-CoV-2 infection.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, asymptomatic SARS-CoV-2 infection surveillance visit swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result, either asymptomatic or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result), prior to Visit 2 should receive Vaccination 2 as normal.

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

If a participant becomes eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study.

Placebo recipients who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Dose 2, and will follow the procedures listed in this section for the remainder of their participation in the study. For Phase 2/3 participants, Visit 101 could occur at the same time as the original Visit 4.

8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Confirm the participant originally received only placebo at Vaccination 1/2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 4 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101)

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Record AEs as described in Section 8.3.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record AEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Record SAEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 103 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102)

This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 104 (if any).
- Request the return of the participant's e-diary or assist the participant/participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Inform the participant/participant's parent(s)/legal guardian that his or her study participation has ended.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.17. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) (Subset for Evaluation of Boostability and Protection Against Emerging VOCs)

The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 or a third and potentially a fourth dose of prototype BNT162b2$_{SA}$.

8.17.1. Visit 301 – Vaccination 3: (150 to 210 Days After Visit 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of a third dose of BNT162b2, he or should remain on the Phase 2/3 visit schedule.

Note: This visit can occur on the same day as Visit 4, but all procedures for both visits must be conducted (including collection of all blood samples).

- Confirm that the participant originally received BNT162b2 at Vaccinations 1 and 2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Record nonstudy vaccinations as described in Section 6.5.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 1, 2, 3, 5, and 6 are met and exclusion criteria 1, 3, 5, 8, 10, 11, 12, 13, 15, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.

- Obtain a nasal (midturbinate) swab (collected by site staff).

- Obtain the participant's randomization number and study intervention allocation number using the IRT system. **The IRT system will also assign an additional single participant number; this number will not be used as the primary identifier for the participant, but must be included in the participant's source documents and transcribed into the CRF**. The system will also identify those participants who are to receive a fourth dose; this should be kept blinded until from the participant until Visit 303.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

    - Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

    - Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):

        - Fever ≥39.0°C (≥102.1°F)

        - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)

        - Severe pain at the injection site

        - Any severe systemic event

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.17.2. Visit 302 – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 301)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- The investigator or an authorized designee completes the CRFs.

8.17.3. Visit 303 – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 301)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.

Only if the participant is to receive a further dose of BNT162b2$_{SA}$:

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 1, 2, 3, 5, and 6 are met and exclusion criteria 1, 3, 5, 8, 10, 11, 12, 13, 15, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):

  - Fever ≥39.0°C (≥102.1°F)

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)

  - Severe pain at the injection site

  - Any severe systemic event

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.17.4. Visit 304 – 1-Week Follow-up Visit (Vaccination 4): (6 to 8 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$

- Record AEs as described in Section 8.3.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Discuss contraceptive use as described in Section 10.4.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.5. Visit 305 – 1-Month Follow-up Visit (Vaccination 4): (28 to 35 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.17.6. Visit 306 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 301)

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.17.7. Visit 307 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 301)

This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record latest CD4 count and HIV viral load.
- Request the participant return the e-diary device or assist the participant to delete the application from his or her personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.18. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

8.18.1. Visit 401 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - Provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Fever ≥39.0°C (≥102.1°F).
- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the study intervention accountability records.

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.18.2. Visit 402 – Vaccination 2: (19 to 23 Days After Visit 401)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the study intervention accountability records.

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.18.3. Visit 403 – 1-Week Follow-up Visit (After Vaccination 2): (6 to 8 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- The investigator or an authorized designee completes the CRFs.

8.18.4. Visit 404 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.18.5. Visit 405 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.18.6. Visit 406 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 402)

This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Request the participant return the e-diary device or assist the participant to delete the application from his or her personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.19. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11 until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

accrued to evaluate this objective, whichever is sooner. The surveillance will be conducted per the procedures listed below.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

8.19.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11

Before surveillance begins and any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

The visit should be conducted only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1) and this visit should be temporarily delayed until the symptoms have resolved.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 3 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Record AEs as described in Section 8.3 (only if the participant remains in the AE reporting period; see Section 8.3.1).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Ask the participant to obtain a surveillance self-swab at home in approximately 14 days or schedule an appointment for the participant to return to collect the swab at the site. The swab should be collected only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1).

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.19.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection

This is a repeating swab collection and will be conducted approximately every 14 days until the intensive surveillance period ends.

- Participant collects a self-swab and ships it to the site for assessment at the central laboratory. The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- Complete the source documents with the swab information.

- The investigator or an authorized designee completes the CRFs with the swab information.

8.20. Administration of a Third Dose of BNT162b2 to Participants Who Have Not Previously Received a Third Dose

The opportunity to receive a third dose of BNT162b2 will be offered as part of the study, according to recommendations detailed separately, and available in the electronic study reference portal.

The additional information collected at Visits 501, 502, 503, and 504 will be collected in a supplementary database; further information on the recording of this information will be provided in the study CRF Completion Requirements document.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

8.20.1. Visit 501 – Third Dose of BNT162b2

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant has only received 2 doses of BNT162 as part of the study and not outside. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant (and meets local recommendations/guidelines), vaccination may proceed, even if inclusion criteria are not met (excluding inclusion criterion 6, which must be met in all cases) and exclusion criteria are met (excluding exclusion criterion 12, applicable to vaccines received outside the study only, which must never be met in any case). Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.22).

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.20.2. Visit 502 – 1-Month Follow-up Telephone Contact: (28 to 35 Days After Visit 501)

- Contact the participant/participant's parent(s)/legal guardian by telephone.

- Record AEs as described in Section 8.3.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 501 (if any).

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.20.3. Visit 503 – 6-Month Follow-up Telephone Contact: (175 to 189 Days After Visit 501)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 502 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.20.4. Visit 504 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 501):

This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 503 (if any).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Request the participant return the e-diary device or assist the participant to delete the application from his or her personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.21. Administration of a Fourth (or Fifth) Dose of BNT162b2 to Eligible Participants From Protocol Amendments 13, 14, and 15

The opportunity to receive an additional dose of BNT162b2 will be offered as part of the study. As part of protocol amendment 19, eligible participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 will be offered an additional 30-µg dose of BNT162b2.

The additional information collected at Visits 601, 602, 603, 604, 605, and 606 will be collected in a supplementary database; further information on the recording of this information will be provided in the study CRF Completion Requirements document.

8.21.1. Visit 601 – Dose 4: (At Least 175 Days After Visit 301 or Visit 8a): Only For Those Participants Who Received Dose 3 at Visit 8a or Visit 301

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his/her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant has received Dose 3 of BNT162 at Visit 301 or Visit 8a as part of the study and not outside. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any). (Not collected for Phase 1 participants who received Dose 3 at Visit 8a).

- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant (and meets local recommendations/guidelines), vaccination may proceed, even if inclusion criteria are not met (excluding inclusion criterion 6, which must be met in all cases) and exclusion criteria are met (excluding exclusion criterion 12, applicable to vaccines received outside the study only, which must never be met in any case). Such exceptions should be recorded in the participant's source documents.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Record AEs as described in Section 8.3.

- Obtain a nasal (midturbinate) swab (collected by site staff).

- Obtain the participant's vaccine vial allocation using the IRT system.

- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.

- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.22).

- Schedule to call the participant by telephone for the next study contact.

- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.21.2. Visit 602 – 1-Month Follow-up Telephone Contact: (28 to 35 Days After Visit 601)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 601 (if any). (Not collected for Phase 1 participants who received Dose 3 at Visit 8a)
- Schedule to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.21.3. Visit 603 – 6-Month Follow-up Telephone Contact: (175 to 189 Days After Visit 601)

This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 602 (if any). (Not collected for Phase 1 participants who received Dose 3 at Visit 8a)
- Request that the participant return the e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

8.21.4. Visit 604 – Dose 5: (At Least 175 Days After Visit 303): Only for the Subset of Participants Who Receive Dose 4 at Visit 303

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant has received Dose 4 of BNT162 at Visit 303 as part of the study and not outside. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the recent test performed since their last visit (if any).
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant (and meets local recommendations/guidelines), vaccination may proceed, even if inclusion criteria are not met (excluding inclusion criterion 6, which must be met in all cases) and exclusion criteria are met (excluding exclusion criterion 12 applicable to vaccines received outside the study only, which must never be met in any case). Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.22).

- Schedule to call the participant by telephone for the next study contact.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.21.5. Visit 605 – 1-Month Follow-up Telephone Contact: (28 to 35 Days After Visit 604)

- Contact the participant/participant's parent(s)/legal guardian by telephone.

- Record AEs as described in Section 8.3.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 604 (if any).

- Schedule to call the participant by telephone for the next study contact.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.21.6. Visit 606 – 6-Month Follow-up Telephone Contact: (175 to 189 Days After Visit 601)

This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 605 (if any).
- Request that the participant return the e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.22. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after the third, fourth, or fifth dose of BNT162b2 should be specifically evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis.

In addition to a clinical evaluation, the following should be performed:

- ECG and
- Measurement of the troponin level

If myocarditis or pericarditis is suspected based upon the initial evaluation, the following should also be performed:

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study

Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by all-available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either $VE_1 > 30\%$ or both VE_1 and VE_2 are >30%. The

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

assessment for the primary analysis will be based on posterior probability using a Bayesian model.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated based on the lower bound of the 95% CI. VE will be demonstrated if the lower bound of the 2-sided 95% CI for VE is >20%.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

9.1.2.2.1. Hypothesis for Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2. If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

9.1.2.2.2. Hypotheses for Boostability and Protection Against Emerging SARS-CoV-2 VOCs

The primary and secondary objectives for boostability and protection against emerging VOCs for BNT162b2-experienced participants and BNT162b2-naïve participants will be assessed based on:

- GMRs of SARS-CoV-2 SA and/or reference strain neutralizing titers using a 1.5-fold noninferiority margin. Noninferiority is met if the lower limit of the alpha adjusted CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.8.

- The difference in percentages of participants with seroresponse to SA and/or reference strain using a 10% noninferiority margin. Noninferiority is met if the lower limit of the alpha-adjusted CI for the difference in percentages of participants with seroresponse is >-10%.

Seroresponse is defined as achieving ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

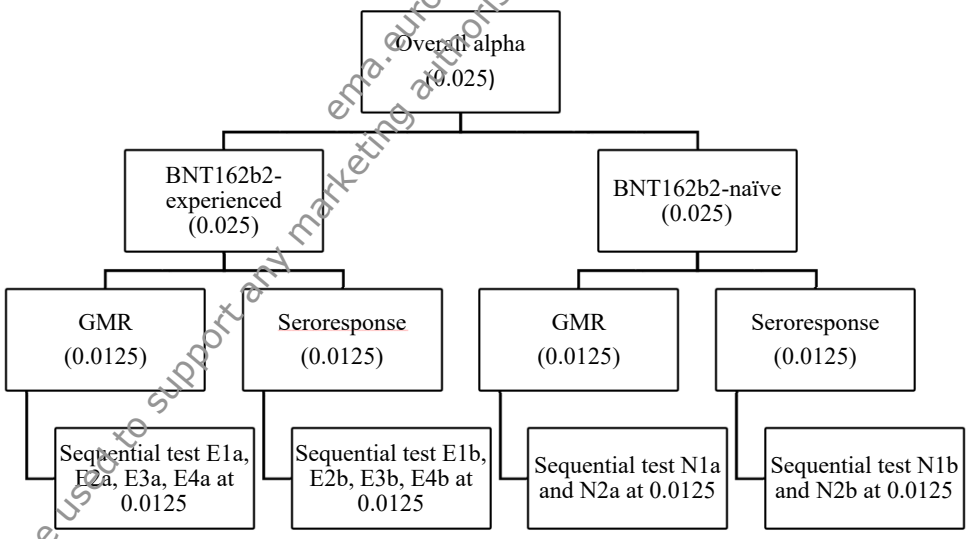
9.1.2.2.2.1. Multiplicity Control for the Boostability and Protection-Against-VOCs Objectives

Figure 1 outlines the type I error control strategy for multiple objectives across different populations (BNT162b2-experienced or BNT162b2-naïve) and estimands (GMR or seroresponse).

The objectives for BNT162b2-experienced participants and BNT162b2-naïve participants will be evaluated independently. The vaccine-experienced and -naïve individuals are different populations with different objectives. The 2 populations are included in the same study to improve operational efficiency. Therefore, no type I error adjustments will be applied to the assessments of the 2 populations.

For each population, the objectives will be evaluated separately for each estimand. To control the overall type I error, the 1-sided alpha of 0.025 will be split and allocated equally to each estimand. Specifically, for each estimand, the hypotheses will be tested in sequential order (as listed in the objectives in Section 3) using a 1-sided alpha of 0.0125 (Figure 1, where E and N represent vaccine-experienced and vaccine-naïve, respectively, and a and b represent GMR and seroresponse estimands, respectively).

Figure 1. Multiplicity Schema



9.2. Sample Size Determination

9.2.1. Phase 1

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

9.2.2. Efficacy Against COVID-19

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

9.2.3. Efficacy Against Asymptomatic Infection

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection will be assessed in Phase 2/3 participants (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT). Assuming a true VE of 70%, a total of 53 asymptomatic cases will provide approximately 90% power to conclude true VE >20%. A total of 206 cases is needed to have 90% power if the true VE is 50%. The hypothesis for asymptomatic seroconversion of N-binding antibody will be tested if at least 206 cases are accrued. The hypothesis for asymptomatic infection based on central laboratory–confirmed NAAT in participants who are consented to participate in the intensive surveillance phase will be tested if at least 53 cases are accrued.

9.2.4. Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 280 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority of adolescents to 16- to 25-year olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.65	-0.2	225	90.4%

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer.

a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).
b. At 0.05 alpha level (2-sided).

9.2.5. Boostability and Protection Against Emerging SARS-CoV-2 VOCs

To assess boostability and protection against emerging SARS-CoV-2 VOCs, approximately 300 participants will be enrolled in each of the 3 groups (BNT162b2-experienced participants to receive either a third dose of BNT162b2 at 30 µg [Group 1] or a third dose of $BNT162b2_{SA}$ [Group 2], BNT162b2-naïve participants to receive 2 doses of $BNT162b2_{SA}$ [Group 3]) to provide an acceptable safety database.

Assuming 20% nonevaluable rate, approximately 240 evaluable participants in each group will contribute to immunogenicity evaluation. This will provide sufficient power for noninferiority evaluations with appropriate multiplicity adjustment for type I error control.

For comparisons based on GMR, the assay standard deviation in log scale is assumed to be 0.74 based on results from Phase 2 of the study and adjusted for assay variability. A GMR of 1 is assumed for each comparison.

For comparisons based on seroresponse, a 90% response rate is assumed for each comparative group or at each comparative time point.

Within-Group Comparison for BNT162b2-Experienced Participants

For each randomized group of BNT162b2-experienced participants (Group 1: received a third dose of BNT162b2 at 30 µg and Group 2: received a third dose of $BNT162b2_{SA}$), with 240 evaluable participants and the stated assumptions for the GMR and standard deviation, the study has >99.9% power to demonstrate NI based on GMR for the objectives in vaccine-experienced individuals using a 1.5-fold margin.

Assuming true response rate of 90% at each time point and 10% of the participants having a different response status at 2 comparative time points, the study has 99% power to show NI based on seroresponse rate for the objectives in vaccine-experienced individuals using a 10% margin. The study will have 89% power to show NI if 20% of the participants have a different response status at 2 comparative time points.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Between-Group Comparison of BNT162b2-Naïve Participants to Selected Existing Phase 3 Participants Who Received 2 Doses of BNT162b2

Approximately 300 participants will be selected from the existing Phase 3 participants who received 2 doses of BNT162b2 to form the control group for the BNT162b2-naïve participants. The selection will ensure comparable distribution of age, sex, and other demographic factors in the control group and BNT162b2-naïve group. With 240 evaluable BNT162b2-naïve participants and 240 evaluable participants in the control group and the above stated assumptions for the GMR, standard deviation, and seroresponse rate, the study has >99.9%% power to declare NI based on GMR for the objectives in vaccine-naïve individuals using a 1.5-fold margin and 89.7% power to declare NI based on seroresponse rate using a 10% margin.

9.2.6. Safety

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=300	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.03	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.06	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.11	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.16	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.21	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.26	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.36	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.45	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.53	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.59	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.65	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.78	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	0.95	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 3 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 (or BNT162b1 for Phase 1) as initially randomized, with Dose 2 received within the predefined window, receive a third dose of BNT162b2 or BNT162b2$_{SA}$ as rerandomized (or receive a third dose of BNT162b2 for Phase 1), have at least 1 valid and determinate immunogenicity result after Dose 3 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 4 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 as initially randomized, with Dose 2 received within the predefined window, receive 2 booster doses of BNT162b2$_{SA}$ as rerandomized, have at least 1 valid and determinate immunogenicity result after Dose 4 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emea-eropean
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Population	Description
Dose 3 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 (or BNT162b1 for Phase 1) at initial randomization, receive a third dose of BNT162b2 or BNT162b2$_{SA}$ at rerandomization (or receive a third dose of BNT162b2 for Phase 1), and have at least 1 valid and determinate immunogenicity result after Dose 3.
Dose 4 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 at initial randomization, receive 2 booster doses of BNT162b2$_{SA}$ at rerandomization, and have at least 1 valid and determinate immunogenicity result after Dose 4.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
Evaluable efficacy (seroconversion)	All eligible randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window, have at least 1 N-binding antibody test result available at a post–Dose 2 visit, and have no other important protocol deviations as determined by the clinician prior to the first post–Dose 2 N-binding antibody test.
Evaluable efficacy (asymptomatic surveillance)	All eligible randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window, consent to participate in the asymptomatic surveillance, and have no other important protocol deviations as determined by the clinician on or before the start of the asymptomatic surveillance period.
All-available efficacy	Dose 1 all-available: All randomized participants who receive at least 1 vaccination. Dose 2 all-available: All randomized participants who complete 2 vaccination doses. Dose 3 all-available: All randomized participants who complete 3 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention. Analyses of reactogenicity endpoints will be based on a subset of the safety population that includes participants with any e-diary data reported after vaccination.
Booster safety	All participants who receive at least 1 booster dose of the study intervention.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Empirical RCDCs will be provided for all immunogenicity analyses.

Endpoint	Statistical Analysis Methods
Primary immunogenicity (Phase 3, boostability and protection against emerging VOCs)	In order to allow direct comparability with the reference strain, the anti-SA NTs may be adjusted to account for intrinsic variant or assay characteristics. The small group of existing Phase 3 participants who are to receive a third and fourth dose of BNT162b2$_{SA}$ will not be included in the primary and secondary analyses except for the last secondary descriptive objective. ***<u>BNT162b2-Experienced Participants:</u>*** **E1a: GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 in the same individuals** **E2a: GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** The comparisons of different NTs (anti-SA or anti–reference strain) or the same NTs at different time points within the same group will be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Endpoint	Statistical Analysis Methods
	limited to participants with nonmissing values at both time points or both NT measurements. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (eg, later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 97.5% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. Noninferiority of E1a and E2a will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8. **E1b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2 in the same individuals** **E2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** Similar to E1a and E2a, the within-group comparisons of seroresponse to different NTs (anti-SA or anti–reference strain) or the same NTs at different time points within the same group will be limited to participants with nonmissing values at both time points or both NT measurements. The percentages of participants with seroresponse at each time point and the difference in percentages will be provided. The 2-sided 97.5% CIs for the difference in percentages of participants with seroresponse will be calculated using the adjusted Wald interval as described by Agresti and Min (2005)[13] for comparing matched proportions. Noninferiority of E1b and E2b will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%. ***BNT162b2-Naïve Participants:*** **N1a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Endpoint	Statistical Analysis Methods
	For the between-group comparison, GMRs will be calculated as the mean of the difference of logarithmically transformed assay results between 2 groups and exponentiating the mean. The associated 2-sided 97.5% CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed titers and exponentiating the confidence limits. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8. **N1b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2** The difference in percentages of participants with seroresponse and associated 2-sided 97.5% CIs will be calculated using the Miettinen and Nurminen method.[14] Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%.
Secondary immunogenicity (Phase 3, boostability and protection against emerging VOCs)	***BNT162b2-Experienced Participants:*** **E3a: GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** **E4a: GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 in the same individuals** **E3b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** **E4b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2 in the same individuals**

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	GMRs and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1a and E2a. If noninferiority of E1a and E2a are both established, E3a and E4a will be assessed sequentially using the same criterion (lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8). The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. Similarly, if noninferiority of E1b and E2b are both established, E3b and E4b will be assessed sequentially using the same criterion (lower bound of the 2-sided 97.5% CI for the difference in percentages is greater than -10%). **GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg** **The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints N1b. **GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** **The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint E1a and E2a.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Endpoint	Statistical Analysis Methods
	The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. ***<u>BNT162b2-Naïve Participants:</u>*** **N2a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2** **N2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2** GMR and the associated 2-sided 97.5% CI will be calculated in the same way as for the primary endpoint N1a. Statistical superiority of N2a will be assessed if noninferiority of N1a is established. Superiority of N2a will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 1. The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints N1b. Statistical superiority of N2b will be assessed if noninferiority of N1b is established. Superiority of N2b will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than 0%. **GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2** **The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints N1b.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Endpoint	Statistical Analysis Methods
Secondary immunogenicity (Phase 1)	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1 and 6 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1 and 6 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Endpoint	Statistical Analysis Methods
	participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1 and 6 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1 and 6 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/ RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the 16- to 25-year age group)	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and 2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment. The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 at least 6 months after the second dose of either BNT162b1 or BNT162b2: **GMTs/GMCs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level** GMTs/GMCs and 2-sided 95% CIs will be provided by initial vaccine and age group for the following time points: • At Dose 3, 7 days and 1 month after Dose 3, and 12 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorization application and/or extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	GMFRs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level GMFRs from before Dose 3 to 7 days and 1 month after Dose 3 and 2-sided 95% CIs will be provided by initial vaccine and age group. GMFRs from before Dose 3 to 12 months after Dose 2 may also be summarized. GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **GMRs of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2** GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed reference-strain titers for each participant (1 month after Dose 3 – 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. **GMRs of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2** GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (SA-variant titer at 1 month after Dose 3 – reference-strain titer at 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Endpoint	Statistical Analysis Methods
Exploratory immunogenicity (Phase 2/3)	**GMTs/GMCs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3: • 1 and 6 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3: • 1 and 6 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels after Dose 1 and after Dose 2.
Exploratory immunogenicity (Phase 3, boostability and protection against emerging VOCs)	**GMTs of SARS-CoV-2 reference strain neutralizing titers in participants receiving a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$** GMTs and associated 2-sided 95% CIs at Dose 3 and each subsequent time point will be provided for each vaccine group and age group. **GMFRs of SARS-CoV-2 reference strain neutralizing titers in participants receiving a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$** GMFRs from Dose 3 to each subsequent time point and associated 2-sided 95% CIs will be provided for each vaccine group and age group. **Geometric mean NT for any VOC not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2** Geometric means and associated 2-sided 95% CIs of any SARS-CoV-2 VOC-neutralizing titers will be provided at each time point for each group.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

9.4.2. Efficacy Analyses

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods

This document cannot be used to support any marketing application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Endpoint	Statistical Analysis Methods
	without the MAR assumption may be explored. The details will be provided in the SAP.
Secondary	**First: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Second: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Third and fourth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Fifth and sixth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints for COVID-19 illness according to CDC-defined symptoms will be evaluated descriptively with 95% CIs. **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group**

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions of variations thereof

Endpoint	Statistical Analysis Methods
	Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days or from 14 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[12] Missing efficacy data will not be imputed. The following secondary efficacy endpoints regarding asymptomatic SARS-CoV-2 infection will be evaluated based on a success criterion of the lower bound of the 2-sided 95% CI for VE being >20%. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate per 1000 person-years of follow-up in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The hypothesis will be tested if at least 206 cases are accrued. In addition, a descriptive summary of VE against asymptomatic infection over different time intervals (ie, prior to 1 month after Dose 2, from 1 month after Dose 2 onward), along with the associated 2-sided 95% CI, will be calculated using the same method. The analysis of the primary definition of asymptomatic cases will be based on the evaluable efficacy (seroconversion) population and the Dose 2 all-available efficacy population. The analysis of the secondary definition of asymptomatic cases will be based on the Dose 1 all-available efficacy population. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants without evidence of infection (up to the**

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any variations or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	start of asymptomatic surveillance period) for the active vaccine group to the placebo group VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The hypothesis will be tested if at least 53 cases are accrued. The analysis will be based on the evaluable efficacy (asymptomatic surveillance) population and the all-available efficacy population and will include only participants who are consented to participate in the asymptomatic surveillance and who do not have serological or virological evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period.
Exploratory	**Ratios of confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants without, and with and without, evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** After the primary objectives are met at the final analysis of at least 164 first primary cases, the study will continue with blinded follow-up until the participant is unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. A descriptive update of VE will be provided with additional follow-up data. VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[12] Supportive analysis of time to confirmed COVID-19 illness will be performed using Kaplan-Meier cumulative incidence curves. Participants who were randomized to placebo will be censored at the time of receipt of BNT162b2. **Incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness after receipt of each dose of

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Endpoint	Statistical Analysis Methods
	BNT162b2 will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with evidence of infection (up to the start of the asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. Participants who are consented to participate in the asymptomatic surveillance and who have serological or virologic evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period will be included in the analysis.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Endpoint	Statistical Analysis Methods
	AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[14] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group. AEs and SAEs reported during the open-label follow-up period will be summarized separately for participants who were unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. For Phase 3 participants enrolled for assessment of boostability and protection against emerging VOCs, descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for local reactions and systemic events from Day 1 through Day 7 after each dose, AEs from Dose 1 to 1 month after the last dose, and SAEs from Dose 1 to 5 or 6 months after the last dose. Local reactions and systemic events from Day 1 through Day 7 after each dose will be presented by severity and cumulatively across severity levels.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Endpoint	Statistical Analysis Methods
	For participants who received the third dose of BNT162b2 as part of protocol amendment 18, descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for AEs and SAEs from Dose 3 to 1 month after Dose 3. For participants who received the fourth (or fifth) dose of BNT162b2 as part of protocol amendment 19, descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for AEs and SAEs from Dose 4 to 1 month after Dose 4 (or Dose 5 to 1 month after Dose 5). The safety analyses after the first dose and after booster dose(s) are based on the safety population and booster safety population, respectively. Analyses of reactogenicity endpoints are based on a subset of the safety population that includes participants with any e-diary data reported after vaccination. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2: Descriptive statistics will be provided by initial vaccine and age group for local reactions and systemic events from Day 1 through Day 7 after Dose 3, and AEs/SAEs from Dose 3 to 1 month after Dose 3. Local reactions and systemic events from Day 1 through Day 7 after Dose 3 will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. For Phase 1 participants who received the fourth dose of BNT162b2 as part of protocol amendment 19, descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for AEs and SAEs from Dose 4 to 1 month after Dose 4.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof emea.europa.eu

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GMFR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

Exploratory analyses to investigate possible immunological correlates with efficacy, and characterization of infecting SARS-CoV-2 variants, may be conducted.

The cell-mediated immune response and additional humoral immune response parameters to the reference strain and SA will be summarized for the subset of participants with PBMC samples collected.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for θ = (1-VE)/(2-VE). The prior is centered at θ = 0.4118 (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 6 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:45)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.

a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8, for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
emea.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

Only the first primary endpoint will be analyzed at IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints (confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and in all participants, confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection and in all participants) will be evaluated sequentially in the stated order, by the same method used for the evaluation of primary VE endpoints. Success thresholds for secondary VE endpoints will be appropriately chosen to control overall type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Complete safety and immunogenicity analysis approximately 1 month after Dose 3 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data (with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.
- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.
- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.
- Safety analyses approximately 1 month after Dose 3 for Phase 3 participants included in the booster evaluation (30 µg or low-dose booster) and approximately 1 month after Dose 2 for newly enrolled Phase 3 participants included in the BNT162b2$_{SA}$ evaluation.
- Immunogenicity analyses approximately 1 month after Dose 3 for Phase 3 participants included in the booster evaluation (30 µg or low-dose booster) and approximately 1 month after Dose 2 for newly enrolled Phase 3 participants included in the BNT162b2$_{SA}$ evaluation, when serology data for the reference strain or for the SA strain are available.
- Analysis of efficacy against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) when a sufficient number of cases have accrued to evaluate the objective(s).
- Complete safety and efficacy analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.
- Safety and efficacy analyses approximately 1 month after the third dose of BNT162b2 for participants who received a third dose of BNT162b2 as part of protocol amendment 18.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Complete safety, efficacy, and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team. Certain analyses may be combined as 1 regulatory submission report if the data become available around the same time. Additional analyses may be conducted if required for regulatory purposes.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met
- Review of safety and/or immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review
- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule

- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Up until the final efficacy analysis, 3 blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial. When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. • Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE/SAE CRF page.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
20vPnC	20-valent pneumococcal conjugate vaccine
Abs	absolute (in Appendix 2)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCR	B-cell receptor
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
E1, E2, etc	vaccine-experienced (statistical tests)
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
ediary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N1, N2, etc	vaccine-naïve (statistical tests)
N/A	not applicable
NAAT	nucleic acid amplification test
NI	noninferiority
non-S	nonspike protein
NT	neutralizing titer
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SA	South Africa
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Abbreviation	Term
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
TCR	T-cell receptor
UK	United Kingdom
ULN	upper limit of normal
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
VOC	variant of concern
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs after accrual of at least 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

10.9. Appendix 9: Genetics

Use/Analysis of DNA and/or RNA

- Genetic variation may impact a participant's response to study intervention, as well as susceptibility to and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA and/or RNA analysis.
- The results of genetic analyses may be reported in a CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA and/or RNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
  - Samples for specified genetic analysis (see Section 8.7) will be stored for up to 15 years or other period as per local requirements.
- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 World Health Organization. COVID-19 weekly epidemiological update – 01 Mar 2022 (who.int). Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---1-march-2022. Accessed: 18 Mar 2022.

4 Centers for Disease Control and Prevention. Emerging SARS-CoV-2 variants. Available from: https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html. Updated: 28 Jan 2021. Accessed: 10 Feb 2021.

5 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

6 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

7 Pfizer. Working to reach everyone, everywhere. Available from: https://www.pfizer.com/science/coronavirus/vaccine/working-to-reach-everyone-everywhere. Accessed: 04 Aug 2022.

8 Ritchie H, Mathieu E, Rodés-Guirao L, et al. Coronavirus pandemic (COVID-19). OurWorldInData.org website. Available from: https://ourworldindata.org/coronavirus. Accessed: 06 Sep 2022.

9 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

10 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

11 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

12 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

13 Agresti A, Min Y. Simple improved confidence intervals for comparing matched proportions. Stat Med 2005;24(5):729-40.

14 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

Document Approval Record

Document Name:	C4591001 Protocol Amendment 20 Clean Copy, 15 Sep 2022
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	16-Sep-2022 03:33:27	Final Approval
PPD	16-Sep-2022 12:22:04	Business Line Approver

090177e19b5013fa\Approved\Approved On: 16-Sep-2022 12:22 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**

Protocol amendment 19	21 March 2022	• Inclusion of an additional 30-µg dose of BNT162b2 for eligible participants from protocol amendments 13-15 who received at least 3 doses of BNT162 in the study.
		  • Added corresponding objectives, estimands, and endpoints.
		  • Added corresponding SoA and procedures.
		  • Added details in the statistical methods sections.
		• Added language to permit early discontinuation of participants for reasons including but not limited to the increased access and availability of BNT162b2 in the real world, reducing the value of participant involvement and observation in this clinical trial.
		• Updated the eligibility window for participants to receive the third (booster) dose under protocol amendment 18 from at least 6 months after Dose 2 to at least 3 months after Dose 2 to provide maximum opportunity to all participants to receive the third dose.
		• Updated the existing objectives, estimands, and endpoints in line with the revised schedule and study duration, and where applicable, removed what is no longer relevant.
		• Clarified AE/SAE collection requirements for participants enrolled under protocol amendments 18 and 19.
		• Updated risk assessment as BNT162b2 is no longer a novel vaccine and there are extensive data available from both clinical trial and real-world settings.

Protocol amendment 18	07 September 2021	• Addition of procedures for monitoring potential myocarditis or pericarditis.
		• Addition of a third dose of BNT162b2 for participants who meet specified recommendations and have not yet received a third dose.
		  • Added corresponding objectives, estimands, and endpoints.
		  • Added corresponding SoA and procedures.
		  • Added details in the statistical methods sections.
		• Added the instruction that participants who receive COVID-19 vaccines outside of the study from protocol amendment 18 onwards should be withdrawn.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 17	20 July 2021	• Changed the analysis method for the within-group comparison of seroresponse rates for Phase 3 booster and VOC immunogenicity assessment from the Miettinen and Nurminen method to the adjusted Wald interval to provide tighter CI and higher power for NI in most cases. • Clarified that any nonstudy coronavirus vaccines are to be recorded at any time they are given during study participation. • Clarified that participants who are randomized in the C4591031 study should be withdrawn from this study.
Protocol amendment 16	28 May 2021	• Removed the requirement to conduct a potential COVID-19 convalescent visit following each potential COVID-19 illness visit. • Clarified that only non-Pfizer interventional studies for prevention of COVID-19 are prohibited throughout study participation. • Clarified that during the 7 days following each vaccination (either as part of this study, co-enrolled C459 studies, or the B7471026 [20vPnC] study), potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. • Revised the noninferiority margin from 2-fold to 1.5-fold and added a minimum GMR point estimate of ≥0.8 as another success criterion for Phase 3 booster and VOC immunogenicity assessment. Noninferiority is met if the lower limit of the alpha-adjusted CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.8. • Added Phase 1 booster participants to the Dose 3 booster immunogenicity population definitions. • Included a booster safety population definition. • Clarified that the interim analyses for booster immunogenicity will be conducted when serology data for the reference strain or for the SA strain are available.
Protocol amendment 15	25 March 2021	• In order to further characterize booster responses induced by BNT162b2, 2 additional lower-dose booster groups have been added to the subset for evaluation of boostability and protection against emerging VOCs. An additional 5-µg or 10-µg dose of BNT162b2 will be given to

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		approximately 144 Phase 3 participants approximately 5 to 7 months after their second dose of BNT162b2. • To further describe cell-mediated immune responses following isolations of PBMCs in a subset of both the Phase 3 participants who receive a single booster vaccination and the BNT162b2-naïve group who receive BNT162b2$_{SA}$, additional genetic testing may also be performed; corresponding details and an appendix have been added. • An exploratory objective was added for Phase 3 participants to describe the immune response to a third dose of BNT162b2 or a third or fourth dose of BNT162b2$_{SA}$ at later time points to align with analyses and corresponding changes detailed in the statistical section. • Removed the lower age limit for eligibility for administration of BNT162b2 to those originally assigned to placebo: this will now be covered in the recommendations detailed separately, and available in the electronic study reference portal. • Allowed administration of BNT162b2 at Visits 101 and 102 to pregnant participants in certain circumstances. • To align with contraception requirements, reduced the EDP reporting period to 28 days after the last dose of study intervention.

Protocol amendment 14	02 March 2021	• In order to further describe duration of protection, and heterologous/homologous protection against the emerging VOCs, an additional dose of BNT162b2 or BNT162b2$_{SA}$ will be given to approximately 600 Phase 3 participants approximately 5 to 7 months after their second dose of BNT162b2; a further dose of BNT162b2$_{SA}$ will be given to approximately 30 of those participants who receive BNT162b2$_{SA}$:
		  • Added corresponding objectives, estimands, and endpoints
		  • Added corresponding SoA and procedures
		  • Added details in the statistical methods sections.
		• Approximately 300 BNT162b2-naïve participants will be enrolled and receive 2 doses of BNT162b2$_{SA}$ to describe heterologous/homologous protection against the emerging VOCs and reference strains:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Added corresponding objectives, estimands, and endpoints • Added corresponding SoA and procedures • Added details in the statistical methods sections. • Cell-mediated immune responses will also be described following isolations of PBMCs in a subset of both the Phase 3 participants who receive a single booster vaccination and the BNT162b2-naïve group who receive $BNT162b2_{SA}$. • Added the asymptomatic case definitions in Section 8.1 and further clarified the secondary definition for asymptomatic case based on seroconversion of N-binding antibody. • Defined the analysis populations used for evaluation of asymptomatic infection based on seroconversion of N-binding antibody and based on NAAT from participants who consent to active surveillance. • Clarified that unblinding for a nonemergency reason should be conducted outside of the IRT system. • Clarified that if multiple visits occur on the same day, all procedures for all visits must be conducted (including collection of all blood samples). • Clarified the plan for stepwise unblinding of the sponsor in the study.
Protocol amendment 13	12 February 2021	• In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2: • Added corresponding objectives, estimands, and endpoints • Added corresponding SoA and procedures • Added details in the statistical methods sections. • Clarified the population used for analysis of reactogenicity endpoints. • To align with current recommendations, investigators may exercise judgment on review of inclusion and exclusion criteria ahead of vaccination with BNT162b2 for participants who originally received placebo.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified that if a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent. • Participants who provide biweekly swabs for surveillance of asymptomatic infection should now continue to swab even after unblinding if they originally received BNT162b2, to maximize the numbers of swabs to be collected. • Clarified the procedures for unscheduled visits to administer a second dose in the event a participant received only 1 dose of BNT162b2.
Protocol amendment 12	14 January 2021	• Because of a formatting error in protocol amendment 11, exclusion criterion 4 was inadvertently added to exclusion criterion 3 and the subsequent criteria renumbered. This amendment corrects that error. • Because of a change in the pace with which participants ≥16 years of age who originally received placebo will become eligible for receipt of BNT162b2, text was updated throughout the protocol to reflect that this will happen in a phased manner, with recommendations detailed separately and available in the electronic study reference portal. • Clarified that participants who are unblinded because they become potentially eligible for receipt of BNT162b2 will not participate in surveillance for asymptomatic SARS CoV-2 infection. • Corrected the exploratory objective to describe non-S seroconversion to SARS-CoV-2 to clarify that this will only include participants who received BNT162b2 at initial randomization (since those who received it subsequently do not have blood drawn). • In line with current recommendations, removed the requirement to discontinue study intervention because of a diagnosis of COVID-19 during the study.
Protocol amendment 11	04 January 2021	• Added approaches to evaluate efficacy against asymptomatic SARS-CoV-2 infection: • Added objectives, estimands, and endpoints, and statistical methods, for assessment via N-binding antibody seroconversion;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**

		• Added a potential intensive surveillance period for nasal swabbing, for assessment via NAAT:
		  • Corresponding objectives, estimands, and endpoints added
		  • Corresponding SoA and procedures added
		  • Details added in the statistical methods sections.
		• Added the possibility of assessing full-length S-binding, instead of S1-binding, IgG levels in Phase 2/3.
		• Clarified in Section 4.1.1 that any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity at the approximate time participants in Phase 2/3 reach Visit 4, for consistency with other sections.
		• Added a sentence to reflect that assent is obtained from participants <18 years of age.

Protocol amendment 10	01 December 2020	• Added the possibility of administering BNT162b2 to participants who originally received placebo, following any local or national recommendations. • Added the possibility of administering BNT162b2 to participants who originally received placebo, following completion of the active safety surveillance period. • Added corresponding exploratory objectives and statistical analysis details. • Removed immunogenicity analyses of titers greater than defined threshold(s). • Removed the need for blinded COVID-19 case review after the final efficacy analysis. • Included the possibility, due to local circumstances related to the COVID-19 pandemic, that study procedures that do not require in-person participant contact may be performed by telehealth. • In light of additional information to better estimate the standard deviation of SARS-CoV-2 neutralizing titers, increased the sample size for the noninferiority immunogenicity analysis in adolescents 12 to 15 years of age.
Protocol amendment 9	29 October 2020	• To better align with the natural history of SARS-CoV-2 infection, added Phase 2/3 secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days after the second dose; also

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		modified the existing secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days, as well as 7 days, after the second dose; • Made corresponding changes to the study design, study assessments and procedures, and statistical analysis sections. • For operational reasons, removed the interim analysis planned after accrual of 32 cases. • Clarified that interim analyses will be conducted after accrual of *at least* 62, 92, and 120 cases. • Included any participants 16 through 17 years of age enrolled under this amendment in the reactogenicity subset. • Added an unblinded clinical scientist to support DMC activities. • Clarified that serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.
Protocol amendment 8	15 October 2020	• Removed "N-binding antibody" and "SARS-CoV-2 detection by NAAT" as endpoints from the third exploratory objective, as these results are used for the determination of the population, and are not endpoints. • Clarified that the "Process 1" participants included in the descriptive analysis of "Process 1"- and "Process 2"-manufactured study interventions will be selected randomly. • Clarified that surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study. • Further modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Clarified that for participants who are not in the reactogenicity subset, local reactions and systemic events following vaccination should be detected and reported as AEs. • Clarified that premenarchal females are not WOCBP. • Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2." • Clarified the degree of unblinding on the unblinded submissions team in Section 6.3.3. • Made provision for a second dose of BNT162b2 in participants who were affected by a medication error at Visit 2 in Section 6.6. • Provided further clarification regarding discontinuation of study intervention in Section 7.1. • Modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Added that 2 periods of potential COVID-19 symptoms within 4 days will be considered as a single illness. • Provided guidance in Section 8.13 regarding circumstances in which a SARS-CoV-2 test might be required even if symptoms within 7 days following each vaccination are considered more likely due to vaccine reactogenicity. • Made allowance in Section 8.13 for a second SARS-CoV-2 test to be performed within the same potential COVID-19 illness if it is in accordance with routine practice. • Added Section 8.15 to describe the reporting of SARS-CoV-2 test results and their implications for participants receiving a second vaccine dose. • Added statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age. • Amended scope of analyses of safety data in Section 9.5.1. • Made various editorial changes.
Protocol amendment 6 (Germany-specific)	23 September 2020	• According to regulatory request, inclusion criterion 1 now specifies that participants less than 18 years of age will not be enrolled in the EU.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 6	08 September 2020	• Reordered some procedures in the Phase 2/3 schedule of activities for consistency with the main body of the protocol. • Corrected the window for the 6-month follow-up visit to be approximately 6 months after Vaccination 2. • Reduced the volume of blood draws to ~20 mL. • Removed the need to have safety data reported for participants to be included in the safety objective assessment. • Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease. • Increased the sample size for Phase 2/3 to ~43,998. • Clarified that inclusion criterion 4 (ie, participants at higher risk for acquiring COVID-19) is applicable for Phase 2/3 only, and provided some examples. • Removed exclusion criterion 2 (ie, known infection with HIV, HCV, or HBV) for Phase 3 and added criteria for HIV-positive participants. • Decreased the lower age limit and removed the upper age limit for inclusion in Phase 2/3 in order to evaluate BNT162b2 30 µg in older adolescents and those over 85 years of age; updated the title and other references to adults to align with this change. • Renamed the immunological assays to align with other program-level documents. • Removed reference to the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) being "heads up." • Clarified that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention. • Added clarification that potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. • Updated the analysis population descriptions to align with the study SAP.
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory. • Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7. • Updated the stopping and alert rule parameters for enhanced COVID-19.
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation, and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol. • To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial • Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	NA

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 24
LIST OF FIGURES 25
1. PROTOCOL SUMMARY 26
1.1. Synopsis 26
1.2. Schema 40
1.3. Schedule of Activities 41
1.3.1. Phase 1 41
1.3.2. Phase 2/3 47
1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo 51
1.3.4. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) (Subset for Evaluation of Boostability and Protection Against Emerging VOCs) 53
1.3.5. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants 56
1.3.6. Surveillance for Asymptomatic SARS-CoV-2 Infection 59
1.3.7. Administration of a Third Dose of BNT162b2 to Participants Who Have Not Previously Received a Third Dose 60
1.3.8. Administration of a Fourth (or Fifth) Dose of BNT162b2 to Eligible Participants From Protocol Amendments 13, 14, and 15 62
2. INTRODUCTION 65
2.1. Study Rationale 65
2.2. Background 65
2.3. Clinical Overview 67
2.4. Benefit/Risk Assessment 67
2.4.1. Risk Assessment 69
2.4.2. Benefit Assessment 70
2.4.3. Overall Benefit/Risk Conclusion 70
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 71
3.1. For Phase 1 71
3.2. For Phase 2/3 73
4. STUDY DESIGN 80
4.1. Overall Design 80

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof once approved

4.1.1. Phase 1 81
4.1.2. Phase 2/3 82
4.2. Scientific Rationale for Study Design 86
4.3. Justification for Dose 86
4.4. End of Study Definition 87
5. STUDY POPULATION 87
5.1. Inclusion Criteria 88
5.2. Exclusion Criteria 89
5.3. Lifestyle Considerations 91
5.3.1. Contraception 91
5.4. Screen Failures 92
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 92
6. STUDY INTERVENTION 93
6.1. Study Intervention(s) Administered 94
6.1.1. Manufacturing Process 94
6.1.2. Administration 95
6.2. Preparation/Handling/Storage/Accountability 96
6.2.1. Preparation and Dispensing 97
6.3. Measures to Minimize Bias: Randomization and Blinding 97
6.3.1. Allocation to Study Intervention 97
6.3.2. Blinding of Site Personnel 97
6.3.3. Blinding of the Sponsor 98
6.3.4. Breaking the Blind 100
6.4. Study Intervention Compliance 100
6.5. Concomitant Therapy 100
6.5.1. Prohibited During the Study 101
6.5.2. Permitted During the Study 102
6.6. Dose Modification 102
6.7. Intervention After the End of the Study 103
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 103

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

7.1. Discontinuation of Study Intervention 103
7.2. Participant Discontinuation/Withdrawal From the Study 104
7.2.1. Withdrawal of Consent 105
7.3. Lost to Follow-up 105
8. STUDY ASSESSMENTS AND PROCEDURES 106
8.1. Efficacy and/or Immunogenicity Assessments 107
8.1.1. Efficacy Against COVID-19 107
8.1.2. Efficacy Against Asymptomatic SARS-CoV-2 Infection 109
8.1.2.1. Seroconversion of N-Binding Antibody 109
8.1.2.2. NAAT-Confirmed SARS-CoV-2 Infection 110
8.1.3. Vaccine-Induced Immunogenicity 110
8.1.4. Biological Samples 110
8.1.5. Surveillance for Asymptomatic SARS-CoV-2 Infection 111
8.2. Safety Assessments 111
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 112
8.2.2. Electronic Diary 112
8.2.2.1. Grading Scales 113
8.2.2.2. Local Reactions 113
8.2.2.3. Systemic Events 114
8.2.2.4. Fever 115
8.2.2.5. Antipyretic Medication 116
8.2.3. Phase 1 Stopping Rules 116
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 117
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 118
8.2.6. Pregnancy Testing 118
8.3. Adverse Events and Serious Adverse Events 118
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 119
8.3.1.1. Reporting SAEs to Pfizer Safety 120
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 121
8.3.2. Method of Detecting AEs and SAEs 121
8.3.3. Follow-up of AEs and SAEs 121

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

8.3.4. Regulatory Reporting Requirements for SAEs....121
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure....122
8.3.5.1. Exposure During Pregnancy....122
8.3.6. Exposure During Breastfeeding....123
8.3.6.1. Occupational Exposure....124
8.3.7. Cardiovascular and Death Events....124
8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs....124
8.3.9. Adverse Events of Special Interest....125
8.3.9.1. Lack of Efficacy....125
8.3.10. Medical Device Deficiencies....125
8.3.11. Medication Errors....125
8.4. Treatment of Overdose....126
8.5. Pharmacokinetics....127
8.6. Pharmacodynamics....127
8.7. Genetics....127
8.8. Biomarkers....127
8.9. Immunogenicity Assessments....127
8.10. Health Economics....127
8.11. Study Procedures....127
8.11.1. Phase 1....128
8.11.1.1. Screening: (0 to 28 Days Before Visit 1)....128
8.11.1.2. Visit 1 – Vaccination 1: (Day 1)....129
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)....131
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)....132
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)....133
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)....135
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)....137

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 138
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4) 138
8.11.1.10. Between Visits 8 and 9 139
8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2) 139
8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a) 141
8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a) 142
8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2 142
8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2 143
8.11.2. Phase 2/3 143
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 143
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 146
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2) 148
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2) 149
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 149
8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 150
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 151
8.13. COVID-19 Surveillance (All Participants) 152
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 153

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit) 154
8.14. Communication and Use of Technology 154
8.15. SARS-CoV-2 NAAT Results 155
8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo 156
8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2) 156
8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101) 157
8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102) 158
8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102) 159
8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102) 160
8.17. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) (Subset for Evaluation of Boostability and Protection Against Emerging VOCs) 160
8.17.1. Visit 301 – Vaccination 3: (150 to 210 Days After Visit 2) 160
8.17.2. Visit 302 – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 301) 162
8.17.3. Visit 303 – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 301) 163
8.17.4. Visit 304 – 1-Week Follow-up Visit (Vaccination 4): (6 to 8 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$ 165
8.17.5. Visit 305 – 1-Month Follow-up Visit (Vaccination 4): (28 to 35 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$ 165
8.17.6. Visit 306 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 301) 166
8.17.7. Visit 307 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 301) 167
8.18. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants 167
8.18.1. Visit 401 – Vaccination 1: (Day 1) 167
8.18.2. Visit 402 – Vaccination 2: (19 to 23 Days After Visit 401) 170

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

8.18.3. Visit 403 – 1-Week Follow-up Visit (After Vaccination 2): (6 to 8 Days After Visit 402) 171
8.18.4. Visit 404 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 402) 172
8.18.5. Visit 405 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 402) 173
8.18.6. Visit 406 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 402) 173
8.19. Surveillance for Asymptomatic SARS-CoV-2 Infection 174
8.19.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11 174
8.19.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection 175
8.20. Administration of a Third Dose of BNT162b2 to Participants Who Have Not Previously Received a Third Dose 176
8.20.1. Visit 501 – Third Dose of BNT162b2 176
8.20.2. Visit 502 – 1-Month Follow-up Telephone Contact: (28 to 35 Days After Visit 501) 178
8.20.3. Visit 503 – 6-Month Follow-up Telephone Contact: (175 to 189 Days After Visit 501) 178
8.20.4. Visit 504 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 501): 179
8.21. Administration of a Fourth (or Fifth) Dose of BNT162b2 to Eligible Participants From Protocol Amendments 13, 14, and 15 179
8.21.1. Visit 601 – Dose 4: (At Least 175 Days After Visit 301 or Visit 8a): Only For Those Participants Who Received Dose 3 at Visit 8a or Visit 301 179
8.21.2. Visit 602 – 1-Month Follow-up Telephone Contact: (28 to 35 Days After Visit 601) 181
8.21.3. Visit 603 – 6-Month Follow-up Telephone Contact: (175 to 189 Days After Visit 601) 182
8.21.4. Visit 604 – Dose 5: (At Least 175 Days After Visit 303): Only for the Subset of Participants Who Receive Dose 4 at Visit 303 182
8.21.5. Visit 605 – 1-Month Follow-up Telephone Contact: (28 to 35 Days After Visit 604) 183

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

8.21.6. Visit 606 – 6-Month Follow-up Telephone Contact: (175 to 189 Days After Visit 601) 184
8.22. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis 184
9. STATISTICAL CONSIDERATIONS 185
9.1. Estimands and Statistical Hypotheses 185
9.1.1. Estimands 185
9.1.2. Statistical Hypotheses 186
9.1.2.1. Statistical Hypothesis Evaluation for Efficacy 186
9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity 186
9.2. Sample Size Determination 188
9.2.1. Phase 1 188
9.2.2. Efficacy Against COVID-19 188
9.2.3. Efficacy Against Asymptomatic Infection 189
9.2.4. Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years 189
9.2.5. Boostability and Protection Against Emerging SARS-CoV-2 VOCs 189
9.2.6. Safety 191
9.3. Analysis Sets 192
9.4. Statistical Analyses 194
9.4.1. Immunogenicity Analyses 194
9.4.2. Efficacy Analyses 205
9.4.3. Safety Analyses 209
9.4.4. Other Analyses 212
9.5. Interim Analyses 212
9.5.1. Analysis Timing 215
9.6. Data Monitoring Committee or Other Independent Oversight Committee 216
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 218
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 218
10.1.1. Regulatory and Ethical Considerations 218
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 218
10.1.2. Informed Consent Process 219

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.1.3. Data Protection 220
10.1.4. Dissemination of Clinical Study Data 220
10.1.5. Data Quality Assurance 221
10.1.6. Source Documents 223
10.1.7. Study and Site Start and Closure 223
10.1.8. Sponsor's Qualified Medical Personnel 224
10.2. Appendix 2: Clinical Laboratory Tests 225
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 227
10.3.1. Definition of AE 227
10.3.2. Definition of SAE 228
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 230
10.3.4. Reporting of SAEs 233
10.4. Appendix 4: Contraceptive Guidance 234
10.4.1. Male Participant Reproductive Inclusion Criteria 234
10.4.2. Female Participant Reproductive Inclusion Criteria 234
10.4.3. Woman of Childbearing Potential 235
10.4.4. Contraception Methods 236
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 238
10.6. Appendix 6: Abbreviations 240
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 244
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection 247
10.9. Appendix 9: Genetics 248
11. REFERENCES 249

LIST OF TABLES

Table 1. Local Reaction Grading Scale 114
Table 2. Systemic Event Grading Scale 115
Table 3. Scale for Fever 116

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Table 4. Power Analysis for Noninferiority Assessment 189
Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 191
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility.....213
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses.....214
Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall.....214
Table 9. Laboratory Abnormality Grading Scale 225
Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 245
Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 246

LIST OF FIGURES

Figure 1. Multiplicity Schema.....188

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which continues to spread globally at high speed. To date, more than 392 million people have been infected with SARS-CoV-2 and >5.7 million have died, demonstrating an urgent need for efficacious vaccines.

Numerous COVID-19 vaccines are currently in development globally, and several candidate COVID-19 vaccines (eg, mRNA vaccines and adenovirus-vectored vaccines expressing the S protein) have been shown to be efficacious in the prevention of COVID-19 in clinical studies and are now available under temporary or emergency authorizations. BNT162b2, an RNA-based COVID-19 vaccine given as a 2-dose series administered 21 days apart, was shown to be safe and effective in a Phase 1/2/3 study and has received authorizations for temporary or emergency use or marketing authorizations in multiple countries and has been fully licensed for use in individuals 16 years of age and above in the US as of 23 Aug 2021.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 3 antigens:

BNT162b1 (variant RBP020.3): a modRNA encoding the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5);

BNT162b2 (variant RBP020.2): a modRNA encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9);

BNT162b2s01 (variant RBP020.11): a modRNA encoding the P2 S containing South Africa B.1.351 variant–specific mutations, hereafter referred to as BNT162b2$_{SA}$, as a representative variant of concern (VOC).

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and/or efficacy of these prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1 and 6 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults at least 6 months after the second dose of either BNT162b1 or BNT162b2	• GMCs/GMTs at the time of Dose 3, 7 days and 1 month after Dose 3, and 12 months after Dose 2. • GMFRs from before Dose 3 to 7 days and 1 month after Dose 3 and 12 months after Dose 2. • GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2 • GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2 given as a fourth dose at least 6 months after the third dose of BNT162b2 for participants who received a fourth dose as part of protocol amendment 19	In participants receiving a fourth dose of study intervention, the percentage of participants reporting: • AEs and SAEs from Dose 4 to 1 month after Dose 4	• AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
Final approved
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof are not approved by the European Medicines Agency

Objectives[a]	Estimands	Endpoints
To describe the safety and tolerability profile of BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants, or as 2 doses to BNT162b2-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 5 or 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2 given as a third dose at least 3 months after the second dose of BNT162b2 (or BNT162b2$_{SA}$) for participants who received a third dose as part of protocol amendment 18	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • AEs and SAEs from Dose 3 to 1 month after Dose 3	• AEs • SAEs
To describe the safety and tolerability profile of BNT162b2 given as a fourth (or fifth) dose at least 6 months after the third (or fourth) dose of BNT162b2 (or BNT162b2$_{SA}$) for participants who received a fourth (or fifth) dose as part of protocol amendment 19	In participants receiving a fourth (or fifth) dose of study intervention, the percentage of participants reporting: • AEs and SAEs from Dose 4 (or Dose 5) to 1 month after Dose 4 (or Dose 5)	• AEs • SAEs
Primary Immunogenicity ***BNT162b2-experienced participants***		
To demonstrate the noninferiority of the anti–reference strain immune response after a third dose of BNT162b2 at 30 µg compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Objectives[a]	Estimands	Endpoints
BNT162b2-naïve participants		
To demonstrate the noninferiority of the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
BNT162b2-experienced participants		
To demonstrate the noninferiority of the anti-SA immune response after a third dose of BNT162b2 at 30 µg compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Objectives[a]	Estimands	Endpoints
To demonstrate the noninferiority of the anti–reference strain immune response after 1 dose of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ and a third dose of BNT162b2 at 30 µg	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg	SARS-CoV-2 SA NT in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$ or the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ and the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate a statistically greater anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 SA NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
To descriptively compare the anti–reference strain immune response after 2 doses of BNT162b2$_{SA}$ and after 2 doses of BNT162b2	GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Objectives[a]	Estimands	Endpoints
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants after receipt of each dose of BNT162b2: Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT at baseline and 1 and 6 months after Dose 2 and GMFR from baseline to 1 and 6 months after Dose 2	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate and characterize the SARS-CoV-2 isolate in cases of: • Confirmed COVID-19 that occur through approximately 6 months after the second dose • Confirmed severe COVID-19 that occur through approximately 6 months after the second dose		• SARS-CoV-2 neutralizing titers • Identification of SARS-CoV-2 variant(s)
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the immune response to any VOCs not already specified	Geometric mean NT for any VOCs not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2	• SARS-CoV-2 NTs for any VOCs not already specified
To describe the immune response to a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$	• GMTs at Dose 3 and subsequent time points • GMFRs from Dose 3 to subsequent time points	• SARS-CoV-2 reference strain NTs
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and SA in a subset of participants: • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 2 doses to BNT162b2-naïve participants • 7 Days and 1 and 6 months after BNT162b2 given as a third dose to BNT162b2-experienced participants		

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objectives.
b. See Section 6.1.1 for a description of the manufacturing process.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ at 30 µg (based upon the South African variant and hereafter referred to as BNT162b2$_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

As part of protocol amendment 18, to reflect current and anticipated recommendations for COVID-19 vaccine boosters, participants in C4591001 who meet specified recommendations (detailed separately and available in the electronic study portal) and have not already received one, will be offered a third dose of BNT162b2 after their second dose of BNT162. This opportunity is only for those participants who received their first 2 doses of BNT162 (including BNT162b1, BNT162b2, or BNT162b2$_{SA}$) as part of the study.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

As part of protocol amendment 19, eligible participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 will be offered an additional 30-µg dose of BNT162b2. BNT162-naïve participants who received 2 primary doses of 30 µg BNT162b2$_{SA}$ under protocol amendment 14 and were enrolled to receive a booster dose at Visit 501 under protocol amendment 18 are not eligible to receive an additional dose.

As part of protocol amendment 19, the study may be terminated early for reasons including but not limited to the increased access and availability of BNT162b2 in the real world, reducing the value of participant involvement and observation in this clinical trial. Further to this, participants who are offered the possibility to participate in a future study within the Pfizer/BioNTech COVID-19 vaccine development program will be discontinued from this study.

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

For evaluation of boostability and protection against emerging VOCs, 600 existing Phase 3 participants 18 to 55 years of age will be rerandomized in a 1:1 ratio to receive either a third dose of BNT162b2 at 30 µg or a third dose of BNT162b2$_{SA}$.

An additional group of 30 existing Phase 3 participants 18 to 55 years of age will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$. For these 30 participants, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the investigator and sponsor will not be. Serum samples from these participants may be used for assay development purposes and, except for objectives relating to response to a fourth dose, their results will be analyzed separately from the main immunogenicity analyses.

A further group of approximately 144 existing Phase 3 participants 18 years of age and older will be enrolled to receive a third, lower, dose of BNT162b2 of either 5 or 10 µg. Approximately 24 participants 18 to 55 years of age and 48 participants >55 years of age will be enrolled in each dose group.

Three hundred participants 18 to 55 years of age who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19 will be enrolled as a new cohort of participants to receive BNT162b2$_{SA}$ given as a 2-dose series.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 5 µg, 10 µg, 20 µg, 30 µg
- BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S containing South Africa B.1.351 variant–specific mutations): 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3 or among participants that are offered the possibility of participating in another study within the Pfizer/BioNTech COVID-19 vaccine development program.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162.

Phase 1/2/3 participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 will be offered an additional dose of BNT162b2 at 30 µg at least 6 months after their last dose of BNT162b2 (or BNT162b2$_{SA}$).

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated. VE will be demonstrated if the lower bound of the 95% CI for VE is >20%.

In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

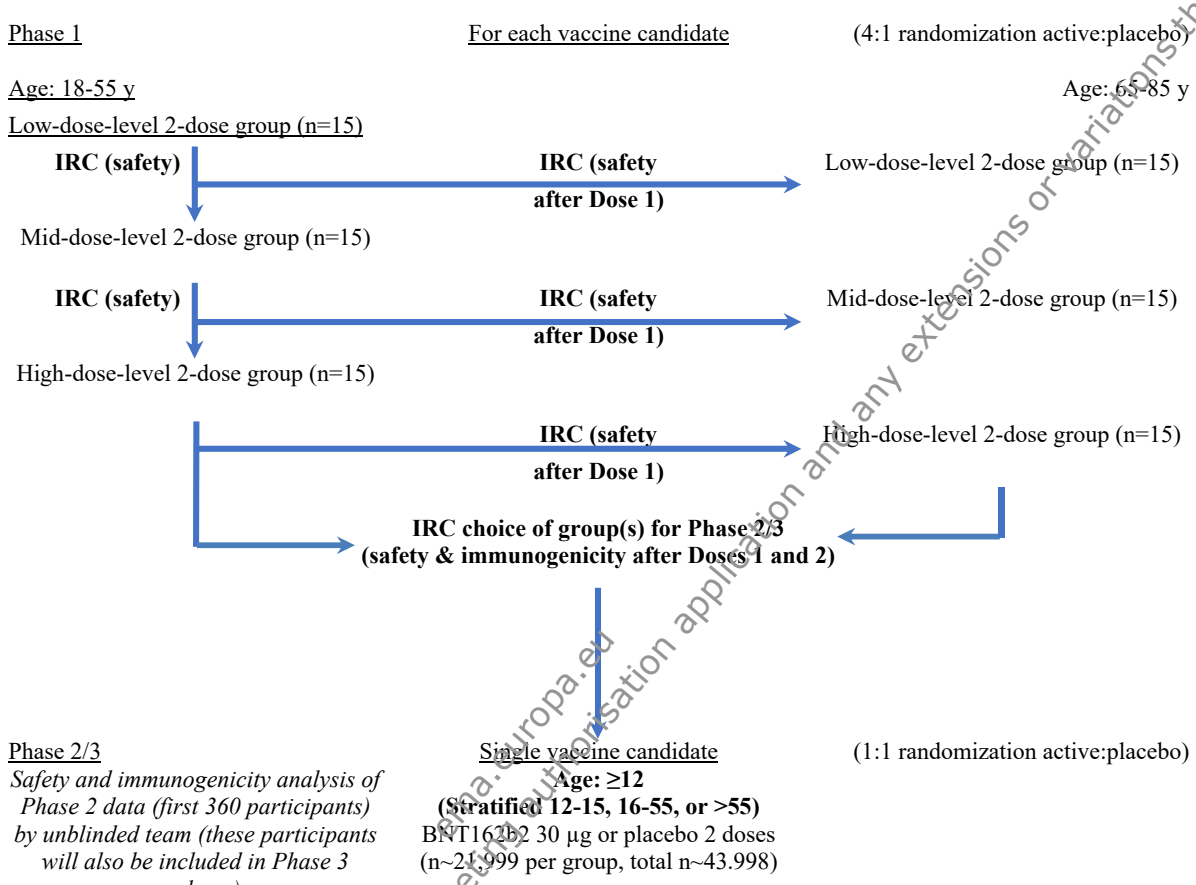
The boostability and protection against emerging VOCs for BNT162b2-experienced participants and BNT162b2-naïve participants will be assessed based on GMRs of SARS-CoV-2 SA-neutralizing and/or reference strain–neutralizing titers using a 1.5-fold noninferiority margin and the difference in percentages of participants with seroresponse using a 10% noninferiority margin.

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

Except for the objectives to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age and evaluation of boostability and protection against emerging VOCs by BNT162b2 and BNT162b2$_{SA}$ in Phase 3, the other immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMR, and the associated 95% CIs, for SARS-CoV-2 neutralizing titers, full-length S-binding or S1-binding IgG levels, and/or RBD-binding IgG levels (Phase 1 only) at the various time points.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

1.2. Schema



Abbreviation: IRC = internal review committee.

Note: Participants who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

1.3. Schedule of Activities

The SoA tables provide an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit is required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected. Prior to protocol amendment 16, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b1 or BNT162b2 (at any dose level) will continue in the study as originally planned.

All other participants will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study no later than at the approximate time participants in Phase 2/3 reach Visit 4. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain informed consent	X								*Continued on table below*	
Assign participant number	X									
Obtain demography and medical history data	X									
Obtain details of medications currently taken	X									
Perform physical examination	X	X	X	X	X	X	X			
Measure vital signs (including body temperature)	X	X	X	X	X	X	X			
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL				
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL									
Serological test for prior COVID-19 infection	~20 mL									
Perform urine pregnancy test (if appropriate)	X	X			X					
Obtain nasal (midturbinate) swab(s)[c]		X			X					X
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X		
Confirm eligibility	X	X			X					
Collect prohibited medication use			X	X	X	X	X	X		X

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Review hematology and chemistry results		X		X	X	X	X		*Continued on table below*	
Review temporary delay criteria		X			X					
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X		
Obtain randomization number and study intervention allocation		X								
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL		
Administer study intervention		X			X					
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X								
Provide thermometer and measuring device		X			X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►	◄	———	►			

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7		Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	***Study procedures for Visit 8 onwards continue on the next table***	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X		*Continued on table below*	
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X		X
Collect e-diary or assist the participant to delete application										
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)										X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	8	8a	8b	8c	9	10	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**		
Obtain informed consent		X					
Confirm participant originally received 10 to 30 µg of BNT162b1 or BNT162b2		X					
Perform urine pregnancy test (if appropriate)		X					
Confirm use of contraceptives (if appropriate)		X	X	X			
Collect prohibited medication use	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X			
Measure body temperature		X					
Confirm eligibility		X					
Review temporary delay criteria		X					
Collect blood sample for immunogenicity assessment	~20 mL	~20 mL	~20 mL	~20 mL	~20 mL		
Obtain nasal (midturbinate) swab(s)		X					X
Obtain the participant's vaccine vial allocation using the IRT system		X					
Administer 30-µg dose of BNT162b2		X					

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Visit Number	8	8a	8b	8c	9	10	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who do not transition from placebo to BNT162b2)**		
Assess acute reactions for at least 30 minutes after study intervention administration		X					
Provide thermometer and measuring device		X					
Remind participant of e-diary technologies		X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		←	→				
Review ongoing reactogenicity e-diary symptoms and obtain stop dates				X			
Collect AEs and SAEs as appropriate	X	X	X	X	X[b]		X
Collect e-diary or assist the participant to delete application						X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: IRT = interactive response technology; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit is required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C. Prior to protocol amendment 16, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b2 or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b2 will continue in the study as originally planned.

All other participants who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4). If they want to receive BNT162b2, they will be unblinded and those who did originally receive placebo will move to the SoA in Section 1.3.3 for their remaining visits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Obtain informed consent	X						
Assign participant number	X						
Obtain demography and medical history data	X						
Perform clinical assessment[c]	X						
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X	
Measure height and weight	X						
Measure temperature (body)	X	X					
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X	X				
Collect nonstudy vaccine information	X	X	X	X			
Collect prohibited medication use		X	X	X	X	X	X
Confirm eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	
Obtain nasal (midturbinate) swab	X	X					X
Obtain randomization number and study intervention allocation	X						
Administer study intervention	X	X					

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X						
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	←	←					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X				
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X
According to eligibility, ascertain willingness to receive BNT162b2 if originally received placebo; if willing, unblind the participant's study intervention assignment (if not already done), and move placebo recipients to the SoA in Section 1.3.3			X	← X			
Collect e-diary or assist the participant to delete application						X	

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. Any placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2.

Visit Number	101	102	103	104	105	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Confirm participant meets local/national recommending criteria or is at least 175 days after Vaccination 2 (Visit 4/Visit 2)	X					
Obtain informed consent	X					
Confirm participant originally received placebo	X					
Perform urine pregnancy test (if appropriate)	X	X				
Confirm use of contraceptives (if appropriate)	X	X				
Collect prohibited medication use	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	
Review and consider eligibility	X	X				
Review temporary delay criteria	X	X				
Collect blood sample for immunogenicity assessment[c]	~20 mL					
Obtain nasal (midturbinate) swab	X	X				X
Obtain vaccine vial allocation via IRT	X	X				
Administer BNT162b2	X	X				
Assess acute reactions for at least 30 minutes after study intervention administration	X	X				

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Visit Number	101	102	103	104	105	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Collect AEs and SAEs as appropriate	X	X	X	X		X[d]
Contact the participant by telephone			X	X	X	
Request the participant return the e-diary or assist the participant to delete the application					X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)						X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

a. For participants who become eligible according to recommendations detailed separately and available in the electronic study reference portal.
b. For any remaining Phase 2/3 placebo recipients who wish to receive BNT162b2; may be combined with Visit 4 for Phase 2/3 participants.
c. Only if the participant has no blood sample collected in the previous 7 days.
d. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.4. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) (Subset for Evaluation of Boostability and Protection Against Emerging VOCs)

Select participants in Phase 3 at select sites who originally received 2 doses of BNT162b2 will be offered the opportunity to receive a third (and potentially fourth) dose of BNT162b2 or BNT162b2$_{SA}$.

Visit Number	301	302	303	304	305	306	307	Unplanned
Visit Description	Vax 3[a]	1-Week Follow-up Visit (After Vax 3)	1-Month Follow-up Visit (After Vax 3)	1-Week Follow-up Visit (After Vax 4)[b]	1-Month Follow-up Visit (After Vax 4)[b]	6-Month Follow-up Visit	18-Month Follow-up Visit	Potential COVID-19 Illness Visit[c]
Visit Window (Days)	150 to 210 Days After Visit 2	6 to 8 Days After Visit 301	28 to 35 Days After Visit 301	6 to 8 Days After Visit 303	28 to 35 Days After Visit 303	175 to 189 Days After Visit 301	532 to 560 Days After Visit 301	Optimally Within 3 Days After Potential COVID-19 Illness Onset
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4				
Obtain informed consent	X							
Confirm participant originally received BNT162b2 at Dose 1 and Dose 2	X							
Perform urine pregnancy test (if appropriate)	X		X[b]					
Confirm use of contraceptives (if appropriate)	X	X	X	X	X			
Collect prohibited medication use	X	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X	X	X		
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X			X	X	
Measure body temperature	X		X[b]					
Confirm eligibility	X		X[b]					
Review temporary delay criteria	X		X[b]					

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Visit Number	301	302	303	304	305	306	307	Unplanned
Visit Description	**Vax 3[a]**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**1-Week Follow-up Visit (After Vax 4)[b]**	**1-Month Follow-up Visit (After Vax 4)[b]**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**150 to 210 Days After Visit 2**	**6 to 8 Days After Visit 301**	**28 to 35 Days After Visit 301**	**6 to 8 Days After Visit 303**	**28 to 35 Days After Visit 303**	**175 to 189 Days After Visit 301**	**532 to 560 Days After Visit 301**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			**ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4**				
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation[d]	~120 mL	~120 mL	~120 mL			~120 mL		
Collect blood sample for HLA typing[d]	~5 mL							
Obtain nasal (midturbinate) swab(s)	X		X[b]					X
Obtain randomization number and study intervention allocation using the IRT system	X							
Administer study intervention	X		X[b]					
Assess acute reactions for at least 30 minutes after study intervention administration	X		X[b]					
Provide thermometer and measuring device	X							
Remind participant of e-diary technologies	X		X[b]					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	←	→		↔				
Review ongoing reactogenicity e-diary symptoms and obtain stop dates			X		X			

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	301	302	303	304	305	306	307	Unplanned
Visit Description	**Vax 3[a]**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**1-Week Follow-up Visit (After Vax 4)[b]**	**1-Month Follow-up Visit (After Vax 4)[b]**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**150 to 210 Days After Visit 2**	**6 to 8 Days After Visit 301**	**28 to 35 Days After Visit 301**	**6 to 8 Days After Visit 303**	**28 to 35 Days After Visit 303**	**175 to 189 Days After Visit 301**	**532 to 560 Days After Visit 301**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			**ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4**				
Collect AEs and SAEs as appropriate	X	X	X	X	X	X[e]	X[e]	X
Collect e-diary or assist the participant to delete application							X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)								X

Abbreviations: e-diary = electronic diary; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; vax = vaccination.

a. Visit 301 can occur on the same day as Visit 4, but all procedures for both visits must be conducted (including collection of all blood samples).
b. Only for those participants who will receive Dose 4.
c. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
d. Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants who will receive a third (but not fourth) dose of BNT162b2 at 30 µg or BNT162b2$_{SA}$ at select sites only.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.5. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants

As part of Amendment 14, an additional cohort of BNT162b2-naïve participants will be enrolled to receive BNT162b2$_{SA}$ per the following SoA.

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain informed consent	X						
Assign participant number	X						
Obtain demography and medical history data	X						
Perform clinical assessment[c]	X						
Measure height and weight	X						
Measure temperature (body)	X	X					
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X	X	X			
Collect nonstudy vaccine information	X	X	X	X	X		
Collect prohibited medication use		X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X			X	X	X	
Confirm eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment	~50 mL		~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation[d]	~120 mL		~120 mL	~120 mL	~120 mL		
Collect blood sample for HLA typing[d]	~5 mL						

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain nasal (midturbinate) swab	X	X					X
Obtain the participant's vaccine vial allocation using the IRT system	X	X					
Administer BNT162b2$_{SA}$	X	X					
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X						
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	◄—►	◄—►					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X		X			
Collect AEs and SAEs as appropriate	X	X	X	X	X[e]	X[e]	X
Collect e-diary or assist the participant to delete application						X	

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: e-diary = electronic diary; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; vax = vaccination.

a. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
b. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
c. Including, if indicated, a physical examination.
d. Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants at select sites only.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

1.3.6. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4 or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

Visit Number	201	202 Onward
Visit Description	**Asymptomatic SARS-CoV-2 Infection Surveillance Consent**	**Asymptomatic SARS-CoV-2 Infection Surveillance Swab**
Visit Window (Days)	**From Approval of Protocol Amendment 11**	**Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection**
Obtain informed consent for asymptomatic SARS-CoV-2 infection surveillance	X	
Collect prohibited medication use	X	
Collect blood sample for immunogenicity assessment[a]	~20 mL/~10 mL	
Obtain nasal (midturbinate) swab (self-swab at home or by site staff at an in-person visit)	X	X
Collect AEs and SAEs as appropriate[b]	X	

a. Only if the participant has no blood sample collected in the previous 7 days. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
b. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

1.3.7. Administration of a Third Dose of BNT162b2 to Participants Who Have Not Previously Received a Third Dose

As part of protocol amendment 18, to reflect current and anticipated recommendations for COVID-19 vaccine boosters, participants in C4591001 who have not already received one, will be offered a third dose of BNT162b2 from at least 3 months (84 days) after their second dose of BNT162. The opportunity to receive a third dose of BNT162b2 will be offered as part of the study, according to recommendations detailed separately, and available in the electronic study reference portal. This opportunity is only for those participants who received their first 2 doses of BNT162 (including BNT162b1, BNT162b2, or BNT162b2$_{SA}$) as part of the study.

Once a participant receives a vaccination at Visit 501, all remaining study visits will follow the SoA as set out below.

The additional information collected at Visits 501, 502, 503, and 504 will be collected in a supplementary database; further information on the recording of this information will be provided in the study CRF Completion Requirements document.

Visit Number	501	502	503	504	Unplanned
Visit Description	**Third Dose of BNT162b2**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**12-Month Follow-up Visit**	**Potential COVID-19 Illness Visit**
Visit Window (Days)	**Per Recommendation[a]**	**28 to 35 Days After Visit 501**	**175 to 189 Days After Visit 501**	**350 to 378 Days After Visit 501**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset[b]**
Confirm participant has only received 2 doses of BNT162 as part of the study and not outside the study	X				
Obtain informed consent	X				
Perform urine pregnancy test (if appropriate)	X				
Confirm use of contraceptives (if appropriate)	X				
Collect nonstudy vaccine information[b]	X	X	X		
Collect prohibited medication use[b]	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X	X	X	X	
Review and consider eligibility	X				
Review temporary delay criteria	X				
Collect blood sample for immunogenicity assessment	~20 mL			~20 mL	
Obtain nasal (midturbinate) swab	X				X
Obtain vaccine vial allocation via IRT	X				

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	501	502	503	504	Unplanned
Visit Description	**Third Dose of BNT162b2**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**12-Month Follow-up Visit**	**Potential COVID-19 Illness Visit**
Visit Window (Days)	**Per Recommendation[a]**	**28 to 35 Days After Visit 501**	**175 to 189 Days After Visit 501**	**350 to 378 Days After Visit 501**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset[b]**
Administer BNT162b2	X				
Assess acute reactions for at least 30 minutes after study intervention administration	X				
Collect AEs and SAEs as appropriate[b]	X	X	X		X[c]
Contact the participant by telephone		X	X		
Request the participant return the e-diary device or assist the participant to delete the application				X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)					X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

a. The opportunity to receive a third dose of BNT162b2 will be offered as part of the study, according to recommendations detailed separately, and available in the electronic study reference portal
b. AEs, nonstudy prohibited medications, and information relating to a potential COVID-19 illness will still be recorded in the original study database (see Section 8.3.1).
c. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

1.3.8. Administration of a Fourth (or Fifth) Dose of BNT162b2 to Eligible Participants From Protocol Amendments 13, 14, and 15

As part of protocol amendment 19, eligible participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 will be offered an additional 30-µg dose of BNT162b2. BNT162-naïve participants who received 2 primary doses of 30 µg BNT162b2$_{SA}$ under protocol amendment 14 and were enrolled to receive a booster dose at Visit 501 under protocol amendment 18 are not eligible to receive an additional dose.

The additional information collected at Visits 601, 602, 603, 604, 605, and 606 will be collected in a supplementary database, and on receipt of vaccination, participants will follow the schedule as set out below; further information on the recording of this information will be provided in the study CRF Completion Requirements document.

Visit Number	601	602	603	604	605	606	Unplanned
Visit Description	**Dose 4[a]**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**Dose 5[a]**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**At Least 175 Days After Visit 8a OR Visit 301**	**28 to 35 Days After Visit 601**	**175 to 189 Days After Visit 601**	**At Least 175 Days After Visit 303**	**28 to 35 Days After Visit 604**	**175 to 189 Days After Visit 604**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ADDITIONAL DOSE ONLY FOR THOSE PARTICIPANTS WHO RECEIVED DOSE 3 AT VISIT 8a or VISIT 301; Participants who decline to receive a fourth dose of BNT162b2 will continue to follow schedule of assessments per Section 1.3.1 or 1.3.4 as appropriate.			**ADDITIONAL DOSE ONLY FOR THOSE PARTICIPANTS WHO RECEIVED DOSE 4 at VISIT 303; Participants who decline to receive a fifth dose of BNT162b2 will continue to follow schedule of assessments per Section 1.3.4.**			
Confirm participant has received at least 3 (or 4) prior doses as part of study and not outside and is eligible to receive fourth (or fifth) dose of BNT162b2	X			X			
Obtain informed consent	X			X			
Perform urine pregnancy test (if appropriate)	X			X			

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	601	602	603	604	605	606	Unplanned
Visit Description	**Dose 4[a]**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**Dose 5[a]**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**At Least 175 Days After Visit 8a OR Visit 301**	**28 to 35 Days After Visit 601**	**175 to 189 Days After Visit 601**	**At Least 175 Days After Visit 303**	**28 to 35 Days After Visit 604**	**175 to 189 Days After Visit 604**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ADDITIONAL DOSE ONLY FOR THOSE PARTICIPANTS WHO RECEIVED DOSE 3 AT VISIT 8a or VISIT 301; Participants who decline to receive a fourth dose of BNT162b2 will continue to follow schedule of assessments per Section 1.3.1 or 1.3.4 as appropriate.			**ADDITIONAL DOSE ONLY FOR THOSE PARTICIPANTS WHO RECEIVED DOSE 4 at VISIT 303; Participants who decline to receive a fifth dose of BNT162b2 will continue to follow schedule of assessments per Section 1.3.4.**			
Confirm use of contraceptives (if appropriate)	X			X			
Collect nonstudy vaccine information[c]	X	X		X	X		
Collect prohibited medication use[c]	X	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load[d]	X	X	X	X	X	X	
Review and consider eligibility	X			X			
Review temporary delay criteria	X			X			
Obtain nasal (midturbinate) swab	X			X			X
Obtain vaccine vial allocation via IRT	X			X			
Administer BNT162b2	X			X			
Assess acute reactions for at least 30 minutes after study intervention administration	X			X			
Collect AEs and SAEs as appropriate[c]	X	X		X	X		X[e]
Contact the participant by telephone		X	X		X	X	
Request the participant return the e-diary device or assist the participant to delete the application			X		X	X	

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	601	602	603	604	605	606	Unplanned
Visit Description	**Dose 4[a]**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**Dose 5[a]**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**At Least 175 Days After Visit 8a OR Visit 301**	**28 to 35 Days After Visit 601**	**175 to 189 Days After Visit 601**	**At Least 175 Days After Visit 303**	**28 to 35 Days After Visit 604**	**175 to 189 Days After Visit 604**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ADDITIONAL DOSE ONLY FOR THOSE PARTICIPANTS WHO RECEIVED DOSE 3 AT VISIT 8a or VISIT 301; Participants who decline to receive a fourth dose of BNT162b2 will continue to follow schedule of assessments per Section 1.3.1 or 1.3.4 as appropriate.			**ADDITIONAL DOSE ONLY FOR THOSE PARTICIPANTS WHO RECEIVED DOSE 4 at VISIT 303; Participants who decline to receive a fifth dose of BNT162b2 will continue to follow schedule of assessments per Section 1.3.4.**			
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology; vax = vaccination.

a. Applicable to those eligible participants per protocol amendments 13, 14, and 15 who received Dose 3 at Visit 8a or 301 or Dose 4 at Visit 303.
b. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
c. AEs and SAEs, nonstudy vaccines and prohibited medications, and information relating to a potential COVID-19 illness will still be recorded in the original study database.
d. Not required to be recorded for Phase 1 participants who received Dose 3 at Visit 8a.
e. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. As of 27 February 2022, over 433 million confirmed cases and over 5.9 million deaths have been reported globally, demonstrating an urgent need for efficacious vaccines.[3]

Numerous COVID-19 vaccines are currently in development globally, and several candidate COVID-19 vaccines (eg, mRNA vaccines and adenovirus-vectored vaccines expressing the S protein) have been shown to be efficacious in the prevention of COVID-19 in clinical studies and are now available under temporary or emergency authorizations. BNT162b2, an RNA-based COVID-19 vaccine given as a 2-dose series administered 21 days apart, was shown to be safe and effective in a Phase 1/2/3 study and has received authorizations for temporary or emergency use or marketing authorizations in multiple countries and has been fully licensed for use in individuals 16 years of age and above in the US as of 23 Aug 2021.

As more data about COVID-19 continue to accrue, the potential duration of protection afforded after a wild-type SARS-CoV-2 infection, and by vaccination, remains unknown. In addition, mutated SARS-CoV-2 VOCs have started to emerge, for example in the UK

(known as 20I/501Y.V1, VOC 202012/01, or B.1.1.7), SA (known as 20H/501Y.V2 or B.1.351), and Brazil (known as P.1).[4]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[5,6]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Three SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 3 antigens:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5);
- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9);
- **BNT162b2s01** (variant RBP020.11): nucleoside-modified messenger RNA (modRNA) as above, but encoding the P2 S containing South Africa B.1.351 variant–specific mutations, hereafter referred to as BNT162b2$_{SA}$, as a representative variant of concern (VOC).

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

In light of the unknowns regarding duration of protection, as well as the emerging VOCs, it is important to understand the boostability of BNT162, and potential heterologous protection against emerging VOC(s). A first step to address this will be to study an additional dose of BNT162b2 at 30 µg given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ (based upon the South African variant and hereafter referred to as

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emea-europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

BNT162b2$_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

As part of protocol amendment 18, to reflect current and anticipated recommendations for COVID-19 vaccine boosters, participants in C4591001 who meet specified recommendations and have not already received one, will be offered a third dose of BNT162b2 after their second dose of BNT162b1, BNT162b2 or BNT162b2$_{SA}$. The opportunity to receive a third dose of BNT162b2 will be offered as part of the study, according to recommendations detailed separately, and available in the electronic study reference portal.

As part of protocol amendment 19, Phase 1/2/3 participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 will be offered an additional dose of BNT162b2 at 30 µg at least 6 months after their last dose of BNT162b2 (or BNT162b2$_{SA}$).

2.3. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[7] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[8] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.4. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

COVID-19 complications and severe disease. In addition, with the currently available therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.

- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.

- All participants 12 to 15 years of age will be included in the reactogenicity subset (see Section 8.2.2).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

2.4.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[9]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation applications and any extensions or variations thereof
ema.europa.eu

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Very rare cases of anaphylaxis, myocarditis, and pericarditis have been reported after authorization in recipients of BNT162b2.	Anaphylaxis: Frequency not known. Myocarditis and pericarditis: Very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. These are generally mild cases, and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.	Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 8.22.

2.4.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of an efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.4.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1 and 6 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults at least 6 months after the second dose of either BNT162b1 or BNT162b2	• GMCs/GMTs at the time of Dose 3, 7 days and 1 month after Dose 3, and 12 months after Dose 2 • GMFRs from before Dose 3 to 7 days and 1 month after Dose 3 and 12 months after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels
	• GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers
	• GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2 given as a fourth dose at least 6 months after the third dose of BNT162b2 for participants who received a fourth dose as part of protocol amendment 19	In participants receiving a fourth dose of study intervention, the percentage of participants reporting: • AEs and SAEs from Dose 4 to 1 month after Dose 4	• AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be reused to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
To describe the safety and tolerability profile of BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants, or as 2 doses to BNT162b2-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 5 or 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2 given as a third dose at least 3 months after the second dose of BNT162b2 (or BNT162b2$_{SA}$) for participants who received a third dose as part of protocol amendment 18	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • AEs and SAEs from Dose 3 to 1 month after Dose 3	• AEs • SAEs
To describe the safety and tolerability profile of BNT162b2 given as a fourth (or fifth) dose at least 6 months after the third (or fourth) dose of BNT162b2 (or BNT162b2$_{SA}$) for participants who received a fourth (or fifth) dose as part of protocol amendment 19	In participants receiving a fourth (or fifth) dose of study intervention, the percentage of participants reporting: • AEs and SAEs from Dose 4 (or Dose 5) to 1 month after Dose 4 (or Dose 5)	• AEs • SAEs
Primary Immunogenicity ***BNT162b2-experienced participants***		
To demonstrate the noninferiority of the anti–reference strain immune response after a third dose of BNT162b2 at 30 µg compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu/psp
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Objectives[a]	Estimands	Endpoints
BNT162b2-naïve participants		
To demonstrate the noninferiority of the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
BNT162b2-experienced participants		
To demonstrate the noninferiority of the anti-SA immune response after a third dose of BNT162b2 at 30 µg compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Objectives[a]	Estimands	Endpoints
To demonstrate the noninferiority of the anti–reference strain immune response after 1 dose of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ and a third dose of BNT162b2 at 30 µg	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg	SARS-CoV-2 SA NT in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$ or the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ and the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate a statistically greater anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 SA NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
To descriptively compare the anti–reference strain immune response after 2 doses of BNT162b2$_{SA}$ and after 2 doses of BNT162b2	GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Objectives[a]	Estimands	Endpoints
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants after receipt of each dose of BNT162b2: Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT at baseline and 1 and 6 months after Dose 2 and GMFR from baseline to 1 and 6 months after Dose 2	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate and characterize the SARS-CoV-2 isolate in cases of: • Confirmed COVID-19 that occur through approximately 6 months after the second dose • Confirmed severe COVID-19 that occur through approximately 6 months after the second dose		• SARS-CoV-2 neutralizing titers • Identification of SARS-CoV-2 variant(s)
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the immune response to any VOCs not already specified	Geometric mean NT for any VOCs not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2	• SARS-CoV-2 NTs for any VOCs not already specified
To describe the immune response to a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$	• GMTs at Dose 3 and subsequent time points • GMFRs from Dose 3 to subsequent time points	• SARS-CoV-2 reference strain NTs
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and SA in a subset of participants: • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 2 doses to BNT162b2-naïve participants • 7 Days and 1 and 6 months after BNT162b2 given as a third dose to BNT162b2-experienced participants		

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for description of the manufacturing process.

Up until the final efficacy analysis, this protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ at 30 µg (based upon the South African variant and hereafter referred to as

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

BNT162b2$_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

As part of protocol amendment 19, eligible participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 will be offered an additional 30-µg dose of BNT162b2. BNT162-naïve participants who received 2 primary doses of 30 µg BNT162b2$_{SA}$ under protocol amendment 14 and were enrolled to receive a booster dose at Visit 501 under protocol amendment 18 are not eligible to receive an additional dose.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than at the approximate time participants in Phase 2/3 reach Visit 4.

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This group of participants will also be offered a fourth dose of BNT162b2 at 30 µg at least 6 months after their third dose.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162. A further fourth dose of BNT162b2 at 30 µg will be offered to these participants at least 6 months after their third dose.

Participants are expected to participate for up to a maximum of approximately 26 months.

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 280 participants from each of the 2 age groups (12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those

This document can only be used to support any marketing authorisation application and any extentions or variations thereof
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

For evaluation of boostability and protection against emerging VOCs, 600 existing Phase 3 participants 18 to 55 years of age will be rerandomized in a 1:1 ratio to receive either a third dose of BNT162b2 at 30 µg or a third dose of BNT162b2$_{SA}$.

A further group of approximately 144 existing Phase 3 participants 18 years of age and older will be enrolled to receive a third, lower, dose of BNT162b2 of either 5 or 10 µg. Approximately 24 participants 18 to 55 years of age and 48 participants ≥ 65 years of age will be enrolled in each dose group. An additional group of 30 existing Phase 3 participants 18 to 55 years of age will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$. For these 30 participants, through 1 month after their first dose of BNT162b2$_{SA}$ the participant will be blinded to their vaccine allocation but the investigator and Sponsor will not be. Serum samples from these participants may be used for assay development purposes and, except for objectives relating to response to a fourth dose, their results will be analyzed separately from the main immunogenicity analyses.

Three hundred participants 18 to 55 years of age who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19 will be enrolled as a new cohort of participants to receive BNT162b2$_{SA}$ given as a 2-dose series.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 2/3 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4).

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

The changes to the protocol as part of protocol amendment 14 to assess boostability and homologous/heterologous protection against emerging VOCs allow the evaluation of safety and immunogenicity of BNT162b2$_{SA}$:

- When given as a third dose to C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously (ie, BNT162b2-experienced) and have not experienced COVID-19.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

- In a small separate group of individuals who previously received 2 doses of BNT162b2 followed by 1 dose of BNT162b2$_{SA}$, a second BNT162b2$_{SA}$ dose will also be given 1 month after Dose 1 of BNT162b2$_{SA}$.

- When given as a 2-dose series, separated by 21 days, in newly recruited participants who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19.

In addition, a group of C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously will receive a third dose of BNT162b2.

This approach will allow an evaluation of immunogenicity against the reference ancestral SARS-CoV-2 strain (Wuhan-Hu-1/USA-WA1) and the selected South African VOC, using a noninferiority approach based on neutralizing antibody titers in prior BNT162b2 vaccinees who receive either a homologous boost (with BNT162b2) or a heterologous boost (with BNT162b2$_{SA}$), as well as new vaccinees receiving 2 doses of BNT162b2$_{SA}$.

As part of protocol amendment 18, to reflect current and anticipated recommendations for COVID-19 vaccine boosters, participants in C4591001 who meet specified recommendations (detailed separately and available in the electronic study portal) and have not already received one, will be offered a third dose of BNT162b2 after their second dose of BNT162. The opportunity to receive a third dose of BNT162b2 will be offered as part of the study, according to recommendations detailed separately, and available in the electronic study reference portal. This opportunity is only for those participants who received their first 2 doses of BNT162 (including BNT162b1, BNT162b2, or BNT162b2$_{SA}$) as part of the study.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.6. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
Document created on
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

As part of protocol amendment 19, eligible participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 will be offered an additional 30-µg dose of BNT162b2. BNT162-naive participants who received 2 primary doses of 30 µg BNT162b2$_{SA}$ under protocol amendment 14 and were enrolled to receive a booster dose at Visit 501 under protocol amendment 18 are not eligible to receive an additional dose.

To provide maximum opportunity for all participants to receive the third dose of BNT162b2 under protocol amendment 18, protocol amendment 19 reduces the eligibility window from at least 6 months after Dose 2 to at least 3 months after Dose 2.

As part of protocol amendment 19, the study may be terminated early for reasons including but not limited to the increased access and availability of BNT162b2 in the real world, reducing the value of participant involvement and observation in this clinical trial.

Further to this, participants who are offered the possibility to participate in a future study within the Pfizer/BioNTech COVID-19 vaccine development program will be discontinued from this study.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness visit will occur and, prior to protocol amendment 16, a subsequent convalescent visit would occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization.

   For the boostability and protection-against-VOCs subset:

   - Existing participants enrolled to receive a third dose of BNT162b2 at 30 µg or BNT162b2$_{SA}$; male or female participants between the ages of 18 and 55 years, inclusive, at rerandomization.
   - Newly enrolled participants enrolled to receive 2 doses of BNT162b2$_{SA}$; male or female participants between the ages of 18 and 55 years, inclusive, at enrollment.
   - Existing participants enrolled to receive a third dose of BNT162b2 at 5 or 10 µg; male or female participants ≥18 years at rerandomization.

   - Note that participants <18 years of age cannot be enrolled in the EU.

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

5. **Boostability and protection-against-VOCs existing participant subset only:** Participants who provided a serum sample at Visit 3, with Visit 3 occurring within the protocol-specified window.

Informed Consent:

6. Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - Chronic liver disease

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
- Resident in a long-term facility
- BMI >30 kg/m^2
- Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry through and including 28 days after the last dose of study intervention, with the exception of non-Pfizer interventional studies for prevention of COVID-19, which are prohibited throughout study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;
    - Sore throat;
    - Diarrhea;
    - Vomiting.
2. Receipt of any seasonal or pandemic influenza vaccine within 14 days (not applicable for the third, fourth, or fifth dose of BNT162b2 at Visits 501, 601, or 604, respectively), or any other nonstudy vaccine within 28 days, before study intervention administration.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days (not applicable for the third, fourth, or fifth dose of BNT162b2 at Visits 501, 601, or 604, respectively, or any other nonstudy vaccine within 28 days, after study intervention administration.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 3 investigational RNA vaccine candidates, with the addition of saline placebo, are the 4 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 5 µg, 10 µg, 20 µg, 30 µg
- BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S containing South Africa B.1.351 variant–specific mutations): 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	5-, 10-, 20-, 30-µg	30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. Participants who originally received placebo and accept the offer to receive BNT162b2 at defined points as part of the study will receive 1 dose of BNT162b2 at each additional vaccination visit (Visits 101 and 102) in accordance with the study's additional SoA (Section 1.3.3). The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162 at Visit 8a.

Participants in the subset for evaluation of boostability and protection against emerging VOCs will receive either a third dose of BNT162b2 or BNT162b2$_{SA}$ approximately 5 to 7 months after their second dose of BNT162 at Visit 301. Of those who receive BNT162b2$_{SA}$ at Visit 301, a subset will receive a further dose of BNT162b2$_{SA}$ at Visit 303.

BNT162b2-naïve participants who are enrolled under protocol amendment 14 to receive BNT162b2$_{SA}$ will receive 1 dose of study intervention at each vaccination visit, Visits 401 and 402.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

As part of protocol amendment 18, participants who have not yet received a third dose of BNT162b2 may receive one at Visit 501, at least 3 months (84 days) after their second dose of BNT162. The administration of a third dose of BNT162b2 at Visit 501 will be conducted in an open-label manner; therefore, the requirement for an unblinded dispenser/administrator does not apply to this vaccination.

As part of protocol amendment 19, eligible participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 may receive an additional dose of 30 µg BNT162b2 at Visit 601 or 604, at least 6 months after their last dose of BNT162. The administration of a fourth (or fifth) dose of BNT162b2 at Visit 601 or 604 will be conducted in an open-label manner; therefore, the requirement for an unblinded preparer, dispenser, and administrator does not apply to this vaccination.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

9. Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded. The visits added in protocol amendment 19 (Visits 601 through 606) will be conducted in an open-label manner; therefore, the requirement for an unblinded preparer, dispenser, and administrator does not apply to this vaccination.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

To allow administration of BNT162b2 to participants who originally received placebo, site staff will be unblinded to individual participants' original study intervention allocation as the participants become eligible for vaccination under local/national recommendations or from 6 months after the second dose.

For the group of 30 existing Phase 3 participants 18 to 55 years of age who will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the investigator will not be.

The administration of the third and fourth (or fifth) dose of BNT162b2 at Visits 501 and 601 (or 604), respectively, will be conducted in an open-label manner.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).
- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.
- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

- After the formal data release of the final efficacy analysis of at least 164 cases, which is considered the primary completion of the study efficacy objectives, additional statisticians and programmers will become unblinded at the participant level to prepare unblinded analyses and other regulatory activities. A group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study.

- After the study data used for submission become public, the blinded study team will also have access to those data, and become unblinded at a group level.

- When a participant is unblinded for potential receipt of BNT162b2 (if he or she originally received placebo) per Section 8.16, the study team will become unblinded to the participant's original study intervention allocation.

For the group of 30 existing Phase 3 participants 18 to 55 years of age who will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the sponsor will not be.

The study will be unblinded in stages once all ongoing participants either have been individually unblinded or have concluded their 6-month post–Dose 2 or post–Dose 3 study visit, as follows:

- Phase 1 (after Visit 8).

- Phase 2/3, ≥16 years (after Visit 4).

- Phase 3, 12 to 15 years (after Visit 4).

- Original Phase 3 participants rerandomized to assess boostability and protection against emerging VOCs (after Visit 306).

The administration of the third and fourth (or fifth) dose of BNT162b2 at Visits 501 and 601 (or 604), respectively, will be conducted in an open-label manner.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

Instructions on how to unblind participants ahead of administration of BNT162b2 to placebo recipients, or for other, nonemergency reasons, will be provided separately: this unblinding will NOT be performed in the IRT. The date (that the participant becomes aware of study intervention allocation) and reason that the blind was broken must be recorded in the source documentation and CRF.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants). In addition, for Phase 1 participants who go on to receive a third dose of BNT162, concomitant vaccinations will be collected from the time the participant provides informed consent (for receipt of Vaccination 3) through and including Visit 8c (1 month after the third dose). For BNT162-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to the time the participant provides informed consent (for participation in the subset) through and including Visit 306. For BNT162b2-naïve participants, the subset for evaluation of protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to study enrollment through and including Visit 405. For participants who receive a third dose of BNT162b2 at Visit 501, all vaccinations received will be recorded from 28 days prior to the time the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

participant provides informed consent (for receipt of the third dose) through Visit 503. For participants who receive a fourth (or fifth) dose of BNT162b2 at Visit 601 or 604 all vaccinations received will be recorded from 28 days prior to the time the participant provides informed consent for receipt of the fourth (or fifth) dose through 1 month after vaccination (Visit 602 or 605.

- Nonstudy coronavirus vaccines are listed in Section 6.5.1 as prohibited throughout the study and should therefore be recorded at any time they are given during study participation. This includes blinded BNT162b2 vaccine/placebo given in the B7471026 study.

- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention. For participants receiving the third dose of BNT162b2 at Visit 501, or the fourth (or fifth) dose of BNT162b2 at Visit 601 (or 604), the administration of the seasonal and pandemic influenza vaccine is not prohibited.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 and from 28 days prior to Visit 8a to Visit 8 for Phase 1 participants, and from 28 days prior to enrollment to Visit 3 for Phase 2/3 participants). Use is also prohibited for participants in the subset for evaluation of boostability and protection against emerging VOCs, from 28 days prior to Visit 301 to Visit 303/305 and the BNT162b2-naïve participants from 28 days prior to enrollment to Visit 404.

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, for whatever reason, a participant receives only 1 dose of BNT162b2, the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. This opportunity also extends to the third, fourth, and fifth doses of BNT162b2, in the event of an issue with the planned administration. For example, because of a medication error a participant receives only 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa); the participant can return at a later date for the unscheduled visit. In this situation:

- Obtain informed consent.
- Measure the participant's body temperature (only in the event the unscheduled visit is to administer a second, not third, fourth, or fifth dose).
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Unblinded or blinded (depending on time point in the study) site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s). Following protocol amendment 19, the mandatory follow-up period for SAE collection will be at least 1 month after the third dose for all participants enrolled under protocol amendment 18.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

Note: Participants who are randomized in the C4591031 or the BNT162-17 study should be withdrawn from this study.

From protocol amendment 18 onwards, participants who receive COVID-19 vaccines outside of the study should be withdrawn. This does not apply if the nonstudy COVID-19 vaccine was administered prior to site receipt of IRB/EC approval of protocol amendment 18.

As part of protocol amendment 19, the study may be terminated early for reasons including but not limited to the increased access and availability of BNT162b2 in the real world, reducing the value of participant involvement and observation in this clinical trial.

Further to this, participants who are offered the possibility to participate in a future study within the Pfizer/BioNTech COVID-19 vaccine development program will be discontinued from this study.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

If a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately up to: 500 mL for participants in Phase 1, 150 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 670 mL during the 24-month study period.

For those Phase 3 participants enrolled in the subset to receive an additional dose of BNT162b2 or BNT162b2$_{SA}$, the total blood sampling volume for individual participants in this study is approximately up to 310 mL for those who receive 3 doses and 410 mL for those who receive 4 doses. Those participants in the subset who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of approximately up to 795 mL.

For those participants enrolled into the additional cohort (added as part of protocol amendment 14) of BNT162b2-naïve participants who will receive 2 doses of BNT162b2$_{SA}$, the total blood sampling volume for individual participants is approximately up to 250 mL. Those participants in the cohort who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of approximately up to 735 mL.

For all participants, other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

8.1.1. Efficacy Against COVID-19

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[10] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
  - Fever;
  - New or increased cough;
  - New or increased shortness of breath;
  - Chills;
  - New or increased muscle pain;
  - New loss of taste or smell;
  - Sore throat;
  - Diarrhea;
  - Vomiting.

  The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):
  - Fatigue;
  - Headache;
  - Nasal congestion or runny nose;
  - Nausea.
- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction*;
- Admission to an ICU;
- Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

8.1.2. Efficacy Against Asymptomatic SARS-CoV-2 Infection

VE against asymptomatic SARS-CoV-2 infection will be evaluated in 2 ways, through impact on seroconversion of N-binding antibody and impact on NAAT-confirmed SARS-CoV-2 infection, in originally enrolled Phase 2/3 participants not suffering from COVID-19. Data from participants who receive more than 2 doses of BNT162b2 will not be included after they receive a third dose.

8.1.2.1. Seroconversion of N-Binding Antibody

Blood samples for assessment of N-binding antibodies are drawn at multiple scheduled visits. An asymptomatic case of SARS-CoV-2 infection based on seroconversion of N-binding antibody is defined as positive N-binding antibody at a post–Dose 2 visit in participants without serological evidence of infection (determined by negative N-binding antibody) at Visit 1 or virological evidence of infection (determined by negative NAAT result at Visit 1 and Visit 2, and at the time of a potential COVID-19 illness). The requirement for a negative NAAT result at Visit 2 is to focus on assessment of protection against asymptomatic infection after 2 doses of vaccine, to the extent possible in an analysis based on seroconversion of N-binding antibody, recognizing that it is not possible to identify and exclude all asymptomatic infections that occur after Dose 1 and prior to Dose 2.

A secondary definition will be applied without the requirement for a negative NAAT result at Visit 2 to allow assessment of protection after 1 dose of vaccine. A positive N-binding antibody at a postvaccination visit in participants with negative N-binding antibody at Visit 1 and negative NAAT results at Visit 1 and at the time of a potential COVID-19 illness is considered an asymptomatic case.

This document can not be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

8.1.2.2. NAAT-Confirmed SARS-CoV-2 Infection

For participants who consent to participate in an intensive period of surveillance, nasal swabs will be obtained to assess SARS-CoV-2 infection by NAAT (see Section 8.1.5).

An asymptomatic case of NAAT-confirmed SARS-CoV-2 infection is defined as a positive NAAT result on a nasal swab collected during the surveillance period from participants without COVID-19 symptoms at the time the nasal swab was taken, or within 14 days after it. The onset date of the asymptomatic case is the collection date of the first nasal swab that tested positive.

8.1.3. Vaccine-Induced Immunogenicity

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay (reference strain and SA variant)
- Full-length S-binding or S1-binding IgG level assay
- RBD-binding IgG level assay (Phase 1 only)

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

Additional whole blood samples of ~120 mL will be obtained from a group of up to approximately 30 participants in each 30-µg group in the subset for evaluation of boostability and protection against emerging VOCs (both BNT162b2-experienced and BNT162b2-naïve) at select sites for isolation of PBMCs. These samples will be used to describe T-cell responses to emerging VOCs and reference strains. Some of the sample may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs, for understanding the B-cell, T-cell, and antibody repertoires. A blood sample of ~5 mL for HLA typing will also be obtained. Some of the 5-mL blood sample collected for HLA typing may be used for DNA and/or RNA isolation to further characterize HLA type.

8.1.4. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine related assay work supporting vaccine programs. No testing of the participant's DNA will be performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

8.1.5. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.6.

The nasal swabs will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2. For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with Section 8.3.2.

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Certain participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. In addition, participants 16 through 17 years of age enrolled under protocol amendment 9 and onwards will be included in the reactogenicity subset. All other participants, including those who originally received placebo and then received BNT162b2 under protocol amendment 10 and onwards, will not complete a reactogenicity e-diary but will have their local reactions and systemic events detected and reported as AEs in accordance with Section 8.3.2. Phase 1 participants who receive a third dose of BNT162b2 will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage in the reactogenicity e-diary for 7 days following administration of the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

study intervention. Participants in the subset for evaluation of boostability and protection against emerging VOCs (both BNT162b2-experienced and BNT162b2-naïve) will be asked to monitor and record local reactions, systemic events, and antipyretic medication use in the reactogenicity e-diary for 7 days following each administration of the study intervention.

The participants receiving a third, fourth, or fifth dose of BNT162b2 at Visits 501, 601, or 604 will not complete a reactogenicity e-diary following vaccination.

The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[9]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the administration of the second dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema europa eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

Administration of BNT162b2 to pregnant participants at Visits 101 and 102 (participants who originally received placebo and choose to be unblinded and receive BNT162b2) or at Visits 501, 601, and 604 may be considered if there are local or national recommendations for COVID-19 vaccination of pregnant women, and the investigator and participant are in agreement. This overrides the requirements stated in the previous paragraph, and will not be considered as a protocol deviation. However, the EDP should still be reported in accordance with Section 8.3.5.1.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Additionally, for those participants who originally received placebo but go on to receive BNT162b2 at Vaccinations 3 and 4, AEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) through and including Visit 103. SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) to approximately 6 months after the second dose of BNT162b2 (Visit 104).

For Phase 1 participants who go on to receive a third dose of BNT162, AEs and SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccination 3) through and including Visit 8c (1 month after the third dose).

For BNT162b2-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, AEs will be collected from the time the participant provides informed consent (for participation in the subset) through and including Visit 303 for those receiving 1 additional dose and Visit 305 for those who receive 2 additional doses. For both schedules, this equates to collection for up to 1 month after the last dose. SAEs will be collected from the time the participant provides informed consent (for participation in the subset) through and including Visit 306 (5 or 6 months after the last dose, depending upon group).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

For BNT162b2-naïve participants, the subset for evaluation of protection against emerging VOCs, AEs will be collected from the time the participant provides informed consent through and including Visit 404 (1 month after the second dose). SAEs will be collected from the time the participant provides informed consent through and including Visit 405 (6 months after the second dose).

For participants who receive a third dose of BNT162b2 at Visit 501, AEs will be collected from the time the participant provides informed consent (for administration of the third dose of BNT162b2) through Visit 502 (1 month after the third dose of BNT162b2). SAEs will be collected from the time the participant provides informed consent (for administration of the third dose of BNT162b2) through Visit 503 (6 months after the third dose of BNT162b2). Under protocol amendment 19, the mandatory follow-up period for SAE collection will be at least 1 month after the third dose for all participants enrolled under protocol amendment 18.

For participants who receive a fourth (or fifth) dose of BNT162b2 at Visit 601 (or 604), AEs and SAEs will be collected from the time the participant provides informed consent (for administration of the fourth [or fifth] dose of BNT162b2) through Visit 602 (or 605) (1 month after the fourth [or fifth] dose of BNT162b2).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose of study intervention. Beyond 28 days after the last dose of study intervention, any pregnancy that occurs will not be considered EDP for this study.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case by case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.6. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.6.1. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

8.3.7. Cardiovascular and Death Events

Not applicable.

8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.9. Adverse Events of Special Interest

The following events are considered AESIs:

- A confirmed diagnosis of myocarditis or pericarditis. See Section 8.22 for additional procedures for monitoring of potential myocarditis or pericarditis.

8.3.9.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.10. Medical Device Deficiencies

Not applicable.

8.3.11. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Some of the blood samples collected for PBMC isolation and HLA typing may be used for DNA and/or RNA isolation. The DNA and/or RNA samples from the PBMC isolation may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs, for understanding the B-cell, T-cell, and antibody repertoires. The DNA and/or RNA samples from the blood sample for HLA typing may be used to further characterize HLA type.

See Appendix 9 for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

Unless stated otherwise, all study visits are intended to be conducted in person at the study site. If this is not possible, because of local circumstances related to the COVID-19 pandemic, study procedures that do not require in-person participant contact may be performed by telehealth. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Irrespective of the nature of the contact, all visit procedures are expected to be performed on the same day.

As the protocol design includes visits of an unplanned nature, multiple visits may occur on the same day, but all procedures for all visits must be conducted (including collection of all blood samples).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.

- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Between Visits 8 and 9

All participants who have not already been unblinded, no later than at the approximate time participants in Phase 2/3 reach Visit 4, will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, he or she will move to the procedures in Section 8.16.

8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of a third dose of BNT162, his or her next visit should be Visit 9.

- Confirm that the participant originally received 10-µg, 20-µg, or 30-µg doses of BNT162b1 or BNT162b2 at Vaccinations 1 and 2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Record nonstudy vaccinations as described in Section 6.5.
- Measure the participant's body temperature.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Ensure and document that inclusion criteria 2, 3, and 6 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer a 30-µg dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
    - Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
    - Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):
        - Fever ≥39.0°C (≥102.1°F)
        - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)
        - Severe pain at the injection site
        - Any severe systemic event

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
cms.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.

    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

    - Fever ≥39.0°C (≥102.1°F).

    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

    - Severe pain at the injection site.

    - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.

- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).

- Measure the participant's body temperature.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Obtain a nasal (midturbinate) swab (collected by site staff).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.

- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).

- Discuss contraceptive use as described in Section 10.4.

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- The investigator or an authorized designee completes the CRFs.
- If Visit 3 is being conducted under amendment 12 onward: If the participant is eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, determine if he/she is willing to receive BNT162b2 as part of the study. If so, unblind the participant's study intervention assignment, and move placebo recipients to the procedures in Section 8.16.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- If not already unblinded, unblind the participant's study intervention assignment, and move placebo recipients willing to receive BNT162b2 to the procedures in Section 8.16.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

This document cannot be used to support and marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;

- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination (either as part of this study, co-enrolled C459 studies, or the B7471026 [20vPnC] study), potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;

- Fever;

- New or increased cough;

- New or increased shortness of breath;

- Chills;

This document cannot be used to support any marketing authorization application and any extensions or variations thereof

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
  - Symptoms and signs, including
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
    - Significant acute renal, hepatic, or neurologic dysfunction

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

- Clinical diagnosis
- Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.
- Full blood count
- Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
- Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
- Number and type of any healthcare contact; duration of hospitalization and ICU stay
- Death

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

Prior to protocol amendment 16, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol; however, data collected from convalescent visits that occurred prior to protocol amendment 16 will remain part of the study data set.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).

- An alert in the event that the participant is hospitalized.

- Visit reminders.

- Messages of thanks and encouragement from the study team.

- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

8.15. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 or 14 days after receipt of the second dose, depending on the objective) of past SARS-CoV-2 infection.

- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

- Asymptomatic SARS-CoV-2 infection surveillance visits: To determine the incidence of asymptomatic SARS-CoV-2 infection.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, asymptomatic SARS-CoV-2 infection surveillance visit swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result, either asymptomatic or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result), prior to Visit 2 should receive Vaccination 2 as normal.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

If a participant becomes eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study.

Placebo recipients who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Dose 2, and will follow the procedures listed in this section for the remainder of their participation in the study. For Phase 2/3 participants, Visit 101 could occur at the same time as the original Visit 4.

8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant originally received only placebo at Vaccination 1/2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 4 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101)

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Record AEs as described in Section 8.3.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Obtain a nasal (midturbinate) swab (collected by site staff).

- Obtain the participant's vaccine vial allocation using the IRT system.

- Site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment to call the participant by telephone for the next study contact.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.

- Record AEs as described in Section 8.3.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 103 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 104 (if any).
- Request the return of the participant's e-diary or assist the participant/participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Inform the participant/participant's parent(s)/legal guardian that his or her study participation has ended.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) (Subset for Evaluation of Boostability and Protection Against Emerging VOCs)

The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 or a third and potentially a fourth dose of prototype BNT162b2$_{SA}$.

8.17.1. Visit 301 – Vaccination 3: (150 to 210 Days After Visit 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of a third dose of BNT162b2, he or should remain on the Phase 2/3 visit schedule.

Note: This visit can occur on the same day as Visit 4, but all procedures for both visits must be conducted (including collection of all blood samples).

- Confirm that the participant originally received BNT162b2 at Vaccinations 1 and 2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Record nonstudy vaccinations as described in Section 6.5.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 1, 2, 3, 5, and 6 are met and exclusion criteria 1, 3, 5, 8, 10, 11, 12, 13, 15, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. **The IRT system will also assign an additional single participant number; this number will not be used as the primary identifier for the participant, but must be included in the participant's source documents and transcribed into the CRF**. The system will also identify those participants who are to receive a fourth dose; this should be kept blinded until from the participant until Visit 303.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):

  - Fever ≥39.0°C (≥102.1°F)

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)

  - Severe pain at the injection site

  - Any severe systemic event

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.17.2. Visit 302 – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 301)

- Record AEs as described in Section 8.3.

- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.3. Visit 303 – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 301)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Only if the participant is to receive a further dose of BNT162b2$_{SA}$:

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 1, 2, 3, 5, and 6 are met and exclusion criteria 1, 3, 5, 8, 10, 11, 12, 13, 15, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):
  - Fever ≥39.0°C (≥102.1°F)
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)
  - Severe pain at the injection site
  - Any severe systemic event
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.4. Visit 304 – 1-Week Follow-up Visit (Vaccination 4): (6 to 8 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2SA

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.5. Visit 305 – 1-Month Follow-up Visit (Vaccination 4): (28 to 35 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2SA

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.6. Visit 306 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 301)

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.17.7. Visit 307 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 301)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record latest CD4 count and HIV viral load.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.18. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

8.18.1. Visit 401 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Obtain any medical history of clinical significance.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - Provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
    - Severe pain at the injection site.
    - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the study intervention accountability records.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.18.2. Visit 402 – Vaccination 2: (19 to 23 Days After Visit 401)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the study intervention accountability records.

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.18.3. Visit 403 – 1-Week Follow-up Visit (After Vaccination 2): (6 to 8 Days After Visit 402)

- Record AEs as described in Section 8.3.

- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.18.4. Visit 404 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.18.5. Visit 405 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.18.6. Visit 406 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 402)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.19. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11 until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The surveillance will be conducted per the procedures listed below.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

8.19.1. Visit 201 – Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11

Before surveillance begins and any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

The visit should be conducted only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

illness visit should be performed (see Section 8.13.1) and this visit should be temporarily delayed until the symptoms have resolved.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 3 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Record AEs as described in Section 8.3 (only if the participant remains in the AE reporting period; see Section 8.3.1).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Ask the participant to obtain a surveillance self-swab at home in approximately 14 days or schedule an appointment for the participant to return to collect the swab at the site. The swab should be collected only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.19.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection

This is a repeating swab collection and will be conducted approximately every 14 days until the intensive surveillance period ends.

- Participant collects a self-swab and ships it to the site for assessment at the central laboratory. The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof in the European Economic Area

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- Complete the source documents with the swab information.

- The investigator or an authorized designee completes the CRFs with the swab information.

8.20. Administration of a Third Dose of BNT162b2 to Participants Who Have Not Previously Received a Third Dose

The opportunity to receive a third dose of BNT162b2 will be offered as part of the study, according to recommendations detailed separately, and available in the electronic study reference portal.

The additional information collected at Visits 501, 502, 503, and 504 will be collected in a supplementary database; further information on the recording of this information will be provided in the study CRF Completion Requirements document.

8.20.1. Visit 501 – Third Dose of BNT162b2

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant has only received 2 doses of BNT162 as part of the study and not outside. Secondary confirmation by another site staff member is required.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant (and meets local recommendations/guidelines), vaccination may proceed, even if inclusion criteria are not met (excluding inclusion criterion 6, which must be met in all cases) and exclusion criteria are met (excluding exclusion criterion 12, applicable to vaccines received outside the study only, which must never be met in any case). Such exceptions should be recorded in the participant's source documents.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Record AEs as described in Section 8.3.

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.

- Obtain a nasal (midturbinate) swab (collected by site staff).

- Obtain the participant's vaccine vial allocation using the IRT system.

- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.

- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.22).

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

8.20.2. Visit 502 – 1-Month Follow-up Telephone Contact: (28 to 35 Days After Visit 501)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 501 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.20.3. Visit 503 – 6-Month Follow-up Telephone Contact: (175 to 189 Days After Visit 501)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 502 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.20.4. Visit 504 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 501):

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 503 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.21. Administration of a Fourth (or Fifth) Dose of BNT162b2 to Eligible Participants From Protocol Amendments 13, 14, and 15

The opportunity to receive an additional dose of BNT162b2 will be offered as part of the study. As part of protocol amendment 19, eligible participants who received a third dose of BNT162b2 (or BNT162b2$_{SA}$) or a third and fourth dose of BNT162b2$_{SA}$ under protocol amendments 13 to 15 will be offered an additional 30-µg dose of BNT162b2.

The additional information collected at Visits 601, 602, 603, 604, 605, and 606 will be collected in a supplementary database; further information on the recording of this information will be provided in the study CRF Completion Requirements document.

8.21.1. Visit 601 – Dose 4: (At Least 175 Days After Visit 301 or Visit 8a): Only For Those Participants Who Received Dose 3 at Visit 8a or Visit 301

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

be personally dated by the signatory. The investigator or his/her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant has received Dose 3 of BNT162 at Visit 301 or Visit 8a as part of the study and not outside. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any). (Not collected for Phase 1 participants who received Dose 3 at Visit 8a).
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant (and meets local recommendations/guidelines), vaccination may proceed, even if inclusion criteria are not met (excluding inclusion criterion 6, which must be met in all cases) and exclusion criteria are met (excluding exclusion criterion 12, applicable to vaccines received outside the study only, which must never be met in any case). Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.22).
- Schedule to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.21.2. Visit 602 – 1-Month Follow-up Telephone Contact: (28 to 35 Days After Visit 601)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 601 (if any). (Not collected for Phase 1 participants who received Dose 3 at Visit 8a)
- Schedule to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

8.21.3. Visit 603 – 6-Month Follow-up Telephone Contact: (175 to 189 Days After Visit 601)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 602 (if any). (Not collected for Phase 1 participants who received Dose 3 at Visit 8a)
- Request that the participant return the e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.21.4. Visit 604 – Dose 5: (At Least 175 Days After Visit 303): Only for the Subset of Participants Who Receive Dose 4 at Visit 303

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant has received Dose 4 of BNT162 at Visit 303 as part of the study and not outside. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the recent test performed since their last visit (if any).
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant (and meets local recommendations/guidelines),

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

vaccination may proceed, even if inclusion criteria are not met (excluding inclusion criterion 6, which must be met in all cases) and exclusion criteria are met (excluding exclusion criterion 12, applicable to vaccines received outside the study only, which must never be met in any case). Such exceptions should be recorded in the participant's source documents.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.22).
- Schedule to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.21.5. Visit 605 – 1-Month Follow-up Telephone Contact: (28 to 35 Days After Visit 604)

- Contact the participant/participant's parent(s)/legal guardian by telephone.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 604 (if any).
- Schedule to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.21.6. Visit 606 – 6-Month Follow-up Telephone Contact: (175 to 189 Days After Visit 601)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 605 (if any).
- Request that the participant return the e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.22. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after the third, fourth, or fifth dose of BNT162b2 should be specifically evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis.

In addition to a clinical evaluation, the following should be performed:

- ECG and
- Measurement of the troponin level

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

If myocarditis or pericarditis is suspected based upon the initial evaluation, the following should also be performed:

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study

Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by all-available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either VE_1 >30% or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated based on the lower bound of the 95% CI. VE will be demonstrated if the lower bound of the 2-sided 95% CI for VE is >20%.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

9.1.2.2.1. Hypothesis for Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2. If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

9.1.2.2.2. Hypotheses for Boostability and Protection Against Emerging SARS-CoV-2 VOCs

The primary and secondary objectives for boostability and protection against emerging VOCs for BNT162b2-experienced participants and BNT162b2-naïve participants will be assessed based on:

- GMRs of SARS-CoV-2 SA and/or reference strain neutralizing titers using a 1.5-fold noninferiority margin. Noninferiority is met if the lower limit of the alpha-adjusted CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.8.

- The difference in percentages of participants with seroresponse to SA and/or reference strain using a 10% noninferiority margin. Noninferiority is met if the lower limit of the alpha-adjusted CI for the difference in percentages of participants with seroresponse is >-10%.

Seroresponse is defined as achieving ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

9.1.2.2.2.1. Multiplicity Control for the Boostability and Protection-Against-VOCs Objectives

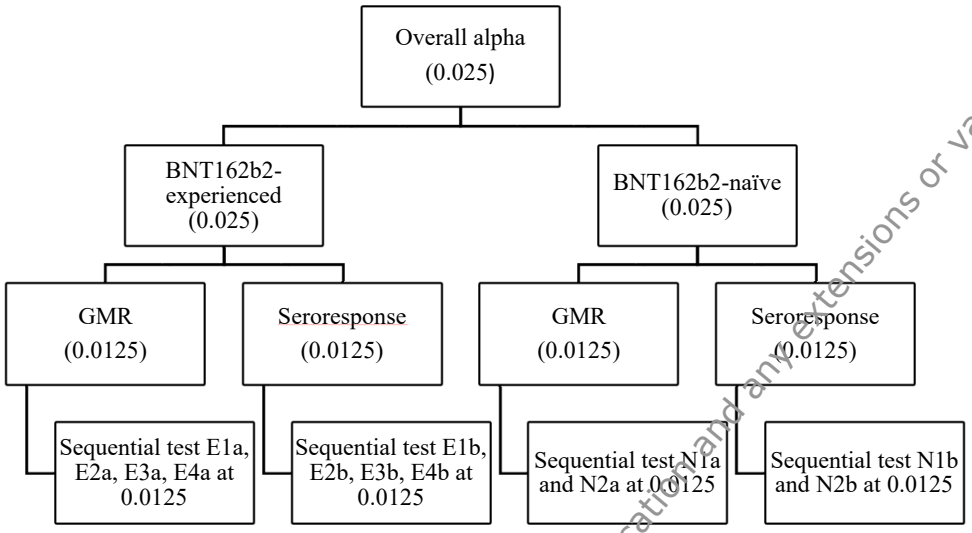
Figure 1 outlines the type I error control strategy for multiple objectives across different populations (BNT162b2-experienced or BNT162b2-naïve) and estimands (GMR or seroresponse).

The objectives for BNT162b2-experienced participants and BNT162b2-naïve participants will be evaluated independently. The vaccine-experienced and -naïve individuals are different populations with different objectives. The 2 populations are included in the same study to improve operational efficiency. Therefore, no type I error adjustments will be applied to the assessments of the 2 populations.

For each population, the objectives will be evaluated separately for each estimand. To control the overall type I error, the 1-sided alpha of 0.025 will be split and allocated equally to each estimand. Specifically, for each estimand, the hypotheses will be tested in sequential order (as listed in the objectives in Section 3) using a 1-sided alpha of 0.0125 (Figure 1, where E and N represent vaccine-experienced and vaccine-naïve, respectively, and a and b represent GMR and seroresponse estimands, respectively).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Figure 1. Multiplicity Schema



9.2. Sample Size Determination

9.2.1. Phase 1

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

9.2.2. Efficacy Against COVID-19

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

9.2.3. Efficacy Against Asymptomatic Infection

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection will be assessed in Phase 2/3 participants (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT). Assuming a true VE of 70%, a total of 53 asymptomatic cases will provide approximately 90% power to conclude true VE >20%. A total of 206 cases is needed to have 90% power if the true VE is 50%. The hypothesis for asymptomatic seroconversion of N-binding antibody will be tested if at least 206 cases are accrued. The hypothesis for asymptomatic infection based on central laboratory–confirmed NAAT in participants who are consented to participate in the intensive surveillance phase will be tested if at least 53 cases are accrued.

9.2.4. Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 280 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.65	-0.2	225	90.4%

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer.
a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).
b. At 0.05 alpha level (2-sided).

9.2.5. Boostability and Protection Against Emerging SARS-CoV-2 VOCs

To assess boostability and protection against emerging SARS-CoV-2 VOCs, approximately 300 participants will be enrolled in each of the 3 groups (BNT162b2-experienced participants to receive either a third dose of BNT162b2 at 30 µg [Group 1] or a third dose of BNT162b2$_{SA}$ [Group 2], BNT162b2-naïve participants to receive 2 doses of BNT162b2$_{SA}$ [Group 3]) to provide an acceptable safety database.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Assuming 20% nonevaluable rate, approximately 240 evaluable participants in each group will contribute to immunogenicity evaluation. This will provide sufficient power for noninferiority evaluations with appropriate multiplicity adjustment for type I error control.

For comparisons based on GMR, the assay standard deviation in log scale is assumed to be 0.74 based on results from Phase 2 of the study and adjusted for assay variability. A GMR of 1 is assumed for each comparison.

For comparisons based on seroresponse, a 90% response rate is assumed for each comparative group or at each comparative time point.

Within-Group Comparison for BNT162b2-Experienced Participants

For each randomized group of BNT162b2-experienced participants (Group 1: received a third dose of BNT162b2 at 30 μg and Group 2: received a third dose of $BNT162b2_{SA}$), with 240 evaluable participants and the stated assumptions for the GMR and standard deviation, the study has >99.9% power to demonstrate NI based on GMR for the objectives in vaccine-experienced individuals using a 1.5-fold margin.

Assuming true response rate of 90% at each time point and 10% of the participants having a different response status at 2 comparative timepoints, the study has 99% power to show NI based on seroresponse rate for the objectives in vaccine-experienced individuals using a 10% margin. The study will have 89% power to show NI if 20% of the participants have a different response status at 2 comparative timepoints.

Between-Group Comparison of BNT162b2-Naïve Participants to Selected Existing Phase 3 Participants Who Received 2 Doses of BNT162b2

Approximately 300 participants will be selected from the existing Phase 3 participants who received 2 doses of BNT162b2 to form the control group for the BNT162b2-naïve participants. The selection will ensure comparable distribution of age, sex, and other demographic factors in the control group and BNT162b2-naïve group. With 240 evaluable BNT162b2-naïve participants and 240 evaluable participants in the control group and the above stated assumptions for the GMR, standard deviation, and seroresponse rate, the study has >99.9%% power to declare NI based on GMR for the objectives in vaccine-naïve individuals using a 1.5-fold margin and 89.7% power to declare NI based on seroresponse rate using a 10% margin.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

9.2.6. Safety

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=300	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.03	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.06	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.11	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.16	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.21	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.26	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.36	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.45	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.53	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.59	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.65	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.78	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	0.95	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 3 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 (or BNT162b1 for Phase 1) as initially randomized, with Dose 2 received within the predefined window, receive a third dose of BNT162b2 or BNT162b2$_{SA}$ as rerandomized (or receive a third dose of BNT162b2 for Phase 1), have at least 1 valid and determinate immunogenicity result after Dose 3 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 4 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 as initially randomized, with Dose 2 received within the predefined window, receive 2 booster doses of BNT162b2$_{SA}$ as rerandomized, have at least 1 valid and determinate immunogenicity result after Dose 4 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emea-eropean
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Population	Description
Dose 3 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 (or BNT162b1 for Phase 1) at initial randomization, receive a third dose of BNT162b2 or BNT162b2$_{SA}$ at rerandomization (or receive a third dose of BNT162b2 for Phase 1), and have at least 1 valid and determinate immunogenicity result after Dose 3.
Dose 4 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 at initial randomization, receive 2 booster doses of BNT162b2$_{SA}$ at rerandomization, and have at least 1 valid and determinate immunogenicity result after Dose 4.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
Evaluable efficacy (seroconversion)	All eligible randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window, have at least 1 N-binding antibody test result available at a post–Dose 2 visit, and have no other important protocol deviations as determined by the clinician prior to the first post–Dose 2 N-binding antibody test.
Evaluable efficacy (asymptomatic surveillance)	All eligible randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window, consent to participate in the asymptomatic surveillance, and have no other important protocol deviations as determined by the clinician on or before the start of the asymptomatic surveillance period.
All-available efficacy	Dose 1 all-available: All randomized participants who receive at least 1 vaccination. Dose 2 all-available: All randomized participants who complete 2 vaccination doses. Dose 3 all-available: All randomized participants who complete 3 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention. Analyses of reactogenicity endpoints will be based on a subset of the safety population that includes participants with any e-diary data reported after vaccination.
Booster safety	All participants who receive at least 1 booster dose of the study intervention.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Empirical RCDCs will be provided for all immunogenicity analyses.

Endpoint	Statistical Analysis Methods
Primary immunogenicity (Phase 3, boostability and protection against emerging VOCs)	In order to allow direct comparability with the reference strain, the anti-SA NTs may be adjusted to account for intrinsic variant or assay characteristics. The small group of existing Phase 3 participants who are to receive a third and fourth dose of BNT162b2$_{SA}$ will not be included in the primary and secondary analyses except for the last secondary descriptive objective. ***<u>BNT162b2-Experienced Participants:</u>*** **E1a: GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 in the same individuals** **E2a: GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** The comparisons of different NTs (anti-SA or anti–reference strain) or the same NTs at different time points within the same group will be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Endpoint	Statistical Analysis Methods
	limited to participants with nonmissing values at both time points or both NT measurements. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (eg, later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 97.5% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. Noninferiority of E1a and E2a will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8. **E1b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2 in the same individuals** **E2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** Similar to E1a and E2a, the within-group comparisons of seroresponse to different NTs (anti-SA or anti–reference strain) or the same NTs at different time points within the same group will be limited to participants with nonmissing values at both time points or both NT measurements. The percentages of participants with seroresponse at each time point and the difference in percentages will be provided. The 2-sided 97.5% CIs for the difference in percentages of participants with seroresponse will be calculated using the adjusted Wald interval as described by Agresti and Min (2005)[11] for comparing matched proportions. Noninferiority of E1b and E2b will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%. ***BNT162b2-Naïve Participants:*** **N1a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Endpoint	Statistical Analysis Methods
	For the between-group comparison, GMRs will be calculated as the mean of the difference of logarithmically transformed assay results between 2 groups and exponentiating the mean. The associated 2-sided 97.5% CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed titers and exponentiating the confidence limits. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8. **N1b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2** The difference in percentages of participants with seroresponse and associated 2-sided 97.5% CIs will be calculated using the Miettinen and Nurminen method.[12] Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%.
Secondary immunogenicity (Phase 3, boostability and protection against emerging VOCs)	***BNT162b2-Experienced Participants:*** **E3a: GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** **E4a: GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 in the same individuals** **E3b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** **E4b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2 in the same individuals**

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	GMRs and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1a and E2a. If noninferiority of E1a and E2a are both established, E3a and E4a will be assessed sequentially using the same criterion (lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8). The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. Similarly, if noninferiority of E1b and E2b are both established, E3b and E4b will be assessed sequentially using the same criterion (lower bound of the 2-sided 97.5% CI for the difference in percentages is greater than -10%). **GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg** **The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints N1b. **GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** **The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint E1a and E2a.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Endpoint	Statistical Analysis Methods
	The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. ***<u>BNT162b2-Naïve Participants:</u>*** **N2a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2** **N2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2** GMR and the associated 2-sided 97.5% CI will be calculated in the same way as for the primary endpoint N1a. Statistical superiority of N2a will be assessed if noninferiority of N1a is established. Superiority of N2a will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 1. The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints N1b. Statistical superiority of N2b will be assessed if noninferiority of N1b is established. Superiority of N2b will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than 0%. **GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2** **The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints N1b.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Endpoint	Statistical Analysis Methods
Secondary immunogenicity (Phase 1)	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1 and 6 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1 and 6 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Endpoint	Statistical Analysis Methods
	participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1 and 6 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1 and 6 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/ RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Endpoint	Statistical Analysis Methods
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the 16- to 25-year age group)	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and 2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment. The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 at least 6 months after the second dose of either BNT162b1 or BNT162b2: **GMTs/GMCs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level** GMTs/GMCs and 2-sided 95% CIs will be provided by initial vaccine and age group for the following time points: • At Dose 3, 7 days and 1 month after Dose 3, and 12 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Endpoint	Statistical Analysis Methods
	GMFRs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level GMFRs from before Dose 3 to 7 days and 1 month after Dose 3 and 2-sided 95% CIs will be provided by initial vaccine and age group. GMFRs from before Dose 3 to 12 months after Dose 2 may also be summarized. GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **GMRs of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2** GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed reference-strain titers for each participant (1 month after Dose 3 – 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. **GMRs of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2** GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (SA-variant titer at 1 month after Dose 3 – reference-strain titer at 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Endpoint	Statistical Analysis Methods
Exploratory immunogenicity (Phase 2/3)	**GMTs/GMCs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3: • 1 and 6 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3: • 1 and 6 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Endpoint	Statistical Analysis Methods
	the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels after Dose 1 and after Dose 2.
Exploratory immunogenicity (Phase 3, boostability and protection against emerging VOCs)	**GMTs of SARS-CoV-2 reference strain neutralizing titers in participants receiving a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$** GMTs and associated 2-sided 95% CIs at Dose 3 and each subsequent time point will be provided for each vaccine group and age group. **GMFRs of SARS-CoV-2 reference strain neutralizing titers in participants receiving a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$** GMFRs from Dose 3 to each subsequent time point and associated 2-sided 95% CIs will be provided for each vaccine group and age group. **Geometric mean NT for any VOC not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2** Geometric means and associated 2-sided 95% CIs of any SARS-CoV-2 VOC-neutralizing titers will be provided at each time point for each group.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

9.4.2. Efficacy Analyses

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Endpoint	Statistical Analysis Methods
	specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.
Secondary	**First: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Second: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Third and fourth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Fifth and sixth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints for COVID-19 illness according to CDC-defined symptoms will be evaluated descriptively with 95% CIs. **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Endpoint	Statistical Analysis Methods
	Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days or from 14 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[10] Missing efficacy data will not be imputed. The following secondary efficacy endpoints regarding asymptomatic SARS-CoV-2 infection will be evaluated based on a success criterion of the lower bound of the 2-sided 95% CI for VE being >20%. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate per 1000 person-years of follow-up in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The hypothesis will be tested if at least 206 cases are accrued. In addition, a descriptive summary of VE against asymptomatic infection over different time intervals (ie, prior to 1 month after Dose 2, from 1 month after Dose 2 onward), along with the associated 2-sided 95% CI, will be calculated using the same method. The analysis of the primary definition of asymptomatic cases will be based on the evaluable efficacy (seroconversion) population and the Dose 2 all-available efficacy population. The analysis of the secondary definition of asymptomatic cases will be based on the Dose 1 all-available efficacy population. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants without evidence of infection (up to the start**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Endpoint	Statistical Analysis Methods
	of asymptomatic surveillance period) for the active vaccine group to the placebo group VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The hypothesis will be tested if at least 53 cases are accrued. The analysis will be based on the evaluable efficacy (asymptomatic surveillance) population and the all-available efficacy population and will include only participants who are consented to participate in the asymptomatic surveillance and who do not have serological or virological evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period.
Exploratory	**Ratios of confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants without, and with and without, evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** After the primary objectives are met at the final analysis of at least 164 first primary cases, the study will continue with blinded follow-up until the participant is unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. A descriptive update of VE will be provided with additional follow-up data. VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[10] Supportive analysis of time to confirmed COVID-19 illness will be performed using Kaplan-Meier cumulative incidence curves. Participants who were randomized to placebo will be censored at the time of receipt of BNT162b2. **Incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness after receipt of each dose of

This document cannot be used to support any marketing authorisation applications and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Endpoint	Statistical Analysis Methods
	BNT162b2 will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with evidence of infection (up to the start of the asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. Participants who are consented to participate in the asymptomatic surveillance and who have serological or virologic evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period will be included in the analysis.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Endpoint	Statistical Analysis Methods
	AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[12] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group. AEs and SAEs reported during the open-label follow-up period will be summarized separately for participants who were unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. For Phase 3 participants enrolled for assessment of boostability and protection against emerging VOCs, descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for local reactions and systemic events from Day 1 through Day 7 after each dose, AEs from Dose 1 to 1 month after the last dose, and SAEs from Dose 1 to 5 or 6 months after the last dose. Local reactions and systemic events from Day 1 through Day 7 after each dose will be presented by severity and cumulatively across severity levels.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Endpoint	Statistical Analysis Methods
	For participants who received the third dose of BNT162b2 as part of protocol amendment 18, descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for AEs and SAEs from Dose 3 to 1 month after Dose 3. For participants who received the fourth (or fifth) dose of BNT162b2 as part of protocol amendment 19, descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for AEs and SAEs from Dose 4 to 1 month after Dose 4 (or Dose 5 to 1 month after Dose 5). The safety analyses after the first dose and after booster dose(s) are based on the safety population and booster safety population, respectively. Analyses of reactogenicity endpoints are based on a subset of the safety population that includes participants with any e-diary data reported after vaccination. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2: Descriptive statistics will be provided by initial vaccine and age group for local reactions and systemic events from Day 1 through Day 7 after Dose 3, and AEs/SAEs from Dose 3 to 1 month after Dose 3. Local reactions and systemic events from Day 1 through Day 7 after Dose 3 will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. For Phase 1 participants who received the fourth dose of BNT162b2 as part of protocol amendment 19, descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for AEs and SAEs from Dose 4 to 1 month after Dose 4.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GMFR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" and each lot of "Process 2" will be summarized descriptively. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected randomly for the analysis.

Exploratory analyses to investigate possible immunological correlates with efficacy, and characterization of infecting SARS-CoV-2 variants, may be conducted.

The cell-mediated immune response and additional humoral immune response parameters to the reference strain and SA will be summarized for the subset of participants with PBMC samples collected.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for θ = (1-VE)/(2-VE). The prior is centered at θ = 0.4118 (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 6 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8, for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

Only the first primary endpoint will be analyzed at IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints (confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and in all participants, confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection and in all participants) will be evaluated sequentially in the stated order, by the same method used for the evaluation of primary VE endpoints. Success thresholds for secondary VE endpoints will be appropriately chosen to control overall type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Complete safety and immunogenicity analysis approximately 1 month after Dose 3 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data (with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.
- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.
- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.
- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2.
- Safety analyses approximately 1 month after Dose 3 for Phase 3 participants included in the booster evaluation (30 µg or low-dose booster) and approximately 1 month after Dose 2 for newly enrolled Phase 3 participants included in the BNT162b2$_{SA}$ evaluation.
- Immunogenicity analyses approximately 1 month after Dose 3 for Phase 3 participants included in the booster evaluation (30 µg or low-dose booster) and approximately 1 month after Dose 2 for newly enrolled Phase 3 participants included in the BNT162b2$_{SA}$ evaluation, when serology data for the reference strain or for the SA strain are available.
- Analysis of efficacy against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) when a sufficient number of cases have accrued to evaluate the objective(s).
- Complete safety and efficacy analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Safety and efficacy analyses approximately 1 month after the third dose of BNT162b2 for participants who received a third dose of BNT162b2 as part of protocol amendment 18.

- Complete safety, efficacy, and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team. Certain analyses may be combined as 1 regulatory submission report if the data become available around the same time. Additional analyses may be conducted if required for regulatory purposes.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met
- Review of safety and/or immunogenicity data to:
    - Allow groups of participants of 65 to 85 years of age to proceed
    - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review
- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
    - Whether any groups may not be started
    - Whether any groups may be terminated early
    - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Up until the final efficacy analysis, 3 blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial. When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. • Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE/SAE CRF page.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
20vPnC	20-valent pneumococcal conjugate vaccine
Abs	absolute (in Appendix 2)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCR	B-cell receptor
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
E1, E2, etc	vaccine-experienced (statistical tests)
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N1, N2, etc	vaccine-naïve (statistical tests)
N/A	not applicable
NAAT	nucleic acid amplification test
NI	noninferiority
non-S	nonspike protein
NT	neutralizing titer
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SA	South Africa
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
TCR	T-cell receptor
UK	United Kingdom
ULN	upper limit of normal
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
VOC	variant of concern
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs after accrual of at least 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

10.9. Appendix 9: Genetics

Use/Analysis of DNA and/or RNA

- Genetic variation may impact a participant's response to study intervention, as well as susceptibility to and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA and/or RNA analysis.
- The results of genetic analyses may be reported in a CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA and/or RNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
  - Samples for specified genetic analysis (see Section 8.7) will be stored for up to 15 years or other period as per local requirements.
- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 World Health Organization. COVID-19 weekly epidemiological update – 01 Mar 2022 (who.int). Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---1-march-2022. Accessed: 18 Mar 2022.

4 Centers for Disease Control and Prevention. Emerging SARS-CoV-2 variants. Available from: https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html. Updated: 28 Jan 2021. Accessed: 10 Feb 2021.

5 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

6 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

7 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

8 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

9 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

10 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

11 Agresti A, Min Y. Simple improved confidence intervals for comparing matched proportions. Stat Med 2005;24(5):729-40.

12 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 19 Clean Copy, 21Mar2022
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	21-Mar-2022 17:34:06	Business Line Approver
PPD	21-Mar-2022 18:05:42	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e199ada67d\Approved\Approved On: 21-Mar-2022 18:05 (GMT)

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**

Protocol amendment 18	07 September 2021	• Addition of procedures for monitoring potential myocarditis or pericarditis.
		• Addition of a third dose of BNT162b2 for participants who meet specified recommendations and have not yet received a third dose.
		  • Added corresponding objectives, estimands, and endpoints.
		  • Added corresponding SoA and procedures.
		  • Added details in the statistical methods sections.
		• Added the instruction that participants who receive COVID-19 vaccines outside of the study from protocol amendment 18 onwards should be withdrawn.

Protocol amendment 17	20 July 2021	• Changed the analysis method for the within-group comparison of seroresponse rates for Phase 3 booster and VOC immunogenicity assessment from the Miettinen and Nurminen method to the adjusted Wald interval to provide tighter CI and higher power for NI in most cases. • Clarified that any nonstudy coronavirus vaccines are to be recorded at any time they are given during study participation. • Clarified that participants who are randomized in the C4591031 study should be withdrawn from this study.
Protocol amendment 16	28 May 2021	• Removed the requirement to conduct a potential COVID-19 convalescent visit following each potential COVID-19 illness visit. • Clarified that only non-Pfizer interventional studies for prevention of COVID-19 are prohibited throughout study participation. • Clarified that during the 7 days following each vaccination (either as part of this study, co-enrolled C459 studies, or the B7471026 [20vPnC] study), potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. • Revised the noninferiority margin from 2-fold to 1.5-fold and added a minimum GMR point estimate of ≥0.8 as another success criterion for

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Phase 3 booster and VOC immunogenicity assessment. Noninferiority is met if the lower limit of the alpha-adjusted CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.8. • Added Phase 1 booster participants to the Dose 3 booster immunogenicity population definitions. • Included a booster safety population definition. • Clarified that the interim analyses for booster immunogenicity will be conducted when serology data for the reference strain or for the SA strain are available.
Protocol amendment 15	25 March 2021	• In order to further characterize booster responses induced by BNT162b2, 2 additional lower-dose booster groups have been added to the subset for evaluation of boostability and protection against emerging VOCs. An additional 5-µg or 10-µg dose of BNT162b2 will be given to approximately 144 Phase 3 participants approximately 5 to 7 months after their second dose of BNT162b2. • To further describe cell-mediated immune responses following isolations of PBMCs in a subset of both the Phase 3 participants who receive a single booster vaccination and the BNT162b2-naïve group who receive $BNT162b2_{SA}$, additional genetic testing may also be performed; corresponding details and an appendix have been added. • An exploratory objective was added for Phase 3 participants to describe the immune response to a third dose of BNT162b2 or a third or fourth dose of $BNT162b2_{SA}$ at later time points to align with analyses and corresponding changes detailed in the statistical section. • Removed the lower age limit for eligibility for administration of BNT162b2 to those originally assigned to placebo: this will now be covered in the recommendations detailed separately, and available in the electronic study reference portal. • Allowed administration of BNT162b2 at Visits 101 and 102 to pregnant participants in certain circumstances. • To align with contraception requirements, reduced the EDP reporting period to 28 days after the last dose of study intervention.
Protocol amendment 14	02 March 2021	• In order to further describe duration of protection, and heterologous/homologous protection against the emerging VOCs, an additional dose of BNT162b2 or $BNT162b2_{SA}$

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		will be given to approximately 600 Phase 3 participants approximately 5 to 7 months after their second dose of BNT162b2; a further dose of BNT162b2$_{SA}$ will be given to approximately 30 of those participants who receive BNT162b2$_{SA}$: • Added corresponding objectives, estimands, and endpoints • Added corresponding SoA and procedures • Added details in the statistical methods sections • Approximately 300 BNT162b2-naïve participants will be enrolled and receive 2 doses of BNT162b2$_{SA}$ to describe heterologous/homologous protection against the emerging VOCs and reference strains: • Added corresponding objectives, estimands, and endpoints • Added corresponding SoA and procedures • Added details in the statistical methods sections. • Cell-mediated immune responses will also be described following isolations of PBMCs in a subset of both the Phase 3 participants who receive a single booster vaccination and the BNT162b2-naïve group who receive BNT162b2$_{SA}$. • Added the asymptomatic case definitions in Section 8.1 and further clarified the secondary definition for asymptomatic case based on seroconversion of N-binding antibody. • Defined the analysis populations used for evaluation of asymptomatic infection based on seroconversion of N-binding antibody and based on NAAT from participants who consent to active surveillance. • Clarified that unblinding for a nonemergency reason should be conducted outside of the IRT system. • Clarified that if multiple visits occur on the same day, all procedures for all visits must be conducted (including collection of all blood samples). • Clarified the plan for stepwise unblinding of the sponsor in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**

Protocol amendment 13	12 February 2021	• In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2:
		  • Added corresponding objectives, estimands, and endpoints
		  • Added corresponding SoA and procedures
		  • Added details in the statistical methods sections.
		• Clarified the population used for analysis of reactogenicity endpoints.
		• To align with current recommendations, investigators may exercise judgment on review of inclusion and exclusion criteria ahead of vaccination with BNT162b2 for participants who originally received placebo.
		• Clarified that if a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent.
		• Participants who provide biweekly swabs for surveillance of asymptomatic infection should now continue to swab even after unblinding if they originally received BNT162b2, to maximize the numbers of swabs to be collected.
		• Clarified the procedures for unscheduled visits to administer a second dose in the event a participant received only 1 dose of BNT162b2.

Protocol amendment 12	14 January 2021	• Because of a formatting error in protocol amendment 11, exclusion criterion 4 was inadvertently added to exclusion criterion 3 and the subsequent criteria renumbered. This amendment corrects that error. • Because of a change in the pace with which participants ≥16 years of age who originally received placebo will become eligible for receipt of BNT162b2, text was updated throughout the protocol to reflect that this will happen in a phased manner, with recommendations detailed separately and available in the electronic study reference portal. • Clarified that participants who are unblinded because they become potentially eligible for receipt of BNT162b2 will not participate in

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		surveillance for asymptomatic SARS CoV-2 infection. • Corrected the exploratory objective to describe non-S seroconversion to SARS-CoV-2 to clarify that this will only include participants who received BNT162b2 at initial randomization (since those who received it subsequently do not have blood drawn). • In line with current recommendations, removed the requirement to discontinue study intervention because of a diagnosis of COVID-19 during the study.

Protocol amendment 11	04 January 2021	• Added approaches to evaluate efficacy against asymptomatic SARS-CoV-2 infection:
		  • Added objectives, estimands, and endpoints, and statistical methods, for assessment via N-binding antibody seroconversion;
		  • Added a potential intensive surveillance period for nasal swabbing, for assessment via NAAT:
		  • Corresponding objectives, estimands, and endpoints added
		  • Corresponding SoA and procedures added
		  • Details added in the statistical methods sections.
		• Added the possibility of assessing full-length S-binding, instead of S1-binding, IgG levels in Phase 2/3.
		• Clarified in Section 4.1.1 that any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity at the approximate time participants in Phase 2/3 reach Visit 4, for consistency with other sections.
		• Added a sentence to reflect that assent is obtained from participants <18 years of age.

Protocol amendment 10	01 December 2020	• Added the possibility of administering BNT162b2 to participants who originally received placebo, following any local or national recommendations. • Added the possibility of administering BNT162b2 to participants who originally received placebo, following completion of the active safety surveillance period. • Added corresponding exploratory objectives and statistical analysis details. • Removed immunogenicity analyses of titers greater than defined threshold(s).

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Removed the need for blinded COVID-19 case review after the final efficacy analysis. • Included the possibility, due to local circumstances related to the COVID-19 pandemic, that study procedures that do not require in-person participant contact may be performed by telehealth. • In light of additional information to better estimate the standard deviation of SARS-CoV-2 neutralizing titers, increased the sample size for the noninferiority immunogenicity analysis in adolescents 12 to 15 years of age.
Protocol amendment 9	29 October 2020	• To better align with the natural history of SARS-CoV-2 infection, added Phase 2/3 secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days after the second dose; also modified the existing secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days, as well as 7 days, after the second dose; • Made corresponding changes to the study design, study assessments and procedures, and statistical analysis sections. • For operational reasons, removed the interim analysis planned after accrual of 32 cases. • Clarified that interim analyses will be conducted after accrual of *at least* 62, 92, and 120 cases. • Included any participants 16 through 17 years of age enrolled under this amendment in the reactogenicity subset. • Added an unblinded clinical scientist to support DMC activities. • Clarified that serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.
Protocol amendment 8	15 October 2020	• Removed "N-binding antibody" and "SARS-CoV-2 detection by NAAT" as endpoints from the third exploratory objective, as these results are used for the determination of the population, and are not endpoints. • Clarified that the "Process 1" participants included in the descriptive analysis of "Process 1"- and "Process 2"-manufactured study interventions will be selected randomly. • Clarified that surveillance of potential COVID-19 symptoms should continue even if a

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		participant has a positive SARS-CoV-2 test earlier in the study. • Further modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Clarified that for participants who are not in the reactogenicity subset, local reactions and systemic events following vaccination should be detected and reported as AEs. • Clarified that premenarchal females are not WOCBP. • Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2. • Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing “Process 1” or “Process 2.” • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing “Process 1” and “Process 2.” • Clarified the degree of unblinding on the unblinded submissions team in Section 6.3.3. • Made provision for a second dose of BNT162b2 in participants who were affected by a medication error at Visit 2 in Section 6.6. • Provided further clarification regarding discontinuation of study intervention in Section 7.1. • Modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Added that 2 periods of potential COVID-19 symptoms within 4 days will be considered as a single illness. • Provided guidance in Section 8.13 regarding circumstances in which a SARS-CoV-2 test might be required even if symptoms within 7 days following each vaccination are considered more likely due to vaccine reactogenicity. • Made allowance in Section 8.13 for a second SARS-CoV-2 test to be performed within the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		same potential COVID-19 illness if it is in accordance with routine practice. • Added Section 8.15 to describe the reporting of SARS-CoV-2 test results and their implications for participants receiving a second vaccine dose. • Added statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age. • Amended scope of analyses of safety data in Section 9.5.1. • Made various editorial changes.
Protocol amendment 6 (Germany-specific)	23 September 2020	• According to regulatory request, inclusion criterion 1 now specifies that participants less than 18 years of age will not be enrolled in the EU.
Protocol amendment 6	08 September 2020	• Reordered some procedures in the Phase 2/3 schedule of activities for consistency with the main body of the protocol. • Corrected the window for the 6-month follow-up visit to be approximately 6 months after Vaccination 2. • Reduced the volume of blood draws to ~20 mL. • Removed the need to have safety data reported for participants to be included in the safety objective assessment. • Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease. • Increased the sample size for Phase 2/3 to ~43,998. • Clarified that inclusion criterion 4 (ie, participants at higher risk for acquiring COVID-19) is applicable for Phase 2/3 only, and provided some examples. • Removed exclusion criterion 2 (ie, known infection with HIV, HCV, or HBV) for Phase 3 and added criteria for HIV-positive participants. • Decreased the lower age limit and removed the upper age limit for inclusion in Phase 2/3 in order to evaluate BNT162b2 30 µg in older adolescents and those over 85 years of age; updated the title and other references to adults to align with this change. • Renamed the immunological assays to align with other program-level documents.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Removed reference to the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) being "heads up." • Clarified that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention. • Added clarification that potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. • Updated the analysis population descriptions to align with the study SAP.
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory. • Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7. • Updated the stopping and alert rule parameters for enhanced COVID-19.
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation, and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol. • To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial • Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 23
LIST OF FIGURES 24
1. PROTOCOL SUMMARY 25
1.1. Synopsis 25
1.2. Schema 39
1.3. Schedule of Activities 40
1.3.1. Phase 1 40
1.3.2. Phase 2/3 47
1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo 51
1.3.4. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) (Subset for Evaluation of Boostability and Protection Against Emerging VOCs) 53
1.3.5. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants 56
1.3.6. Surveillance for Asymptomatic SARS-CoV-2 Infection 59
1.3.7. Administration of a Third Dose of BNT162b2 to Participants Who Have Not Previously Received a Third Dose 60
2. INTRODUCTION 62
2.1. Study Rationale 62
2.2. Background 62
2.3. Clinical Overview 64
2.4. Benefit/Risk Assessment 64
2.4.1. Risk Assessment 66
2.4.2. Benefit Assessment 68
2.4.3. Overall Benefit/Risk Conclusion 68
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 68
3.1. For Phase 1 68
3.2. For Phase 2/3 70
4. STUDY DESIGN 77
4.1. Overall Design 77
4.1.1. Phase 1 78
4.1.2. Phase 2/3 79

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof in the European Union

4.2. Scientific Rationale for Study Design 82
4.3. Justification for Dose 83
4.4. End of Study Definition 84
5. STUDY POPULATION 84
5.1. Inclusion Criteria 84
5.2. Exclusion Criteria 85
5.3. Lifestyle Considerations 88
5.3.1. Contraception 88
5.4. Screen Failures 88
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 88
6. STUDY INTERVENTION 89
6.1. Study Intervention(s) Administered 90
6.1.1. Manufacturing Process 90
6.1.2. Administration 91
6.2. Preparation/Handling/Storage/Accountability 92
6.2.1. Preparation and Dispensing 93
6.3. Measures to Minimize Bias: Randomization and Blinding 93
6.3.1. Allocation to Study Intervention 93
6.3.2. Blinding of Site Personnel 93
6.3.3. Blinding of the Sponsor 94
6.3.4. Breaking the Blind 95
6.4. Study Intervention Compliance 96
6.5. Concomitant Therapy 96
6.5.1. Prohibited During the Study 97
6.5.2. Permitted During the Study 97
6.6. Dose Modification 98
6.7. Intervention After the End of the Study 98
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 99
7.1. Discontinuation of Study Intervention 99
7.2. Participant Discontinuation/Withdrawal From the Study 99

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

7.2.1. Withdrawal of Consent 100
7.3. Lost to Follow-up 101
8. STUDY ASSESSMENTS AND PROCEDURES 101
8.1. Efficacy and/or Immunogenicity Assessments 102
8.1.1. Efficacy Against COVID-19 102
8.1.2. Efficacy Against Asymptomatic SARS-CoV-2 Infection 104
8.1.2.1. Seroconversion of N-Binding Antibody 105
8.1.2.2. NAAT-Confirmed SARS-CoV-2 Infection 105
8.1.3. Vaccine-Induced Immunogenicity 105
8.1.4. Biological Samples 106
8.1.5. Surveillance for Asymptomatic SARS-CoV-2 Infection 106
8.2. Safety Assessments 107
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 107
8.2.2. Electronic Diary 108
8.2.2.1. Grading Scales 109
8.2.2.2. Local Reactions 109
8.2.2.3. Systemic Events 110
8.2.2.4. Fever 111
8.2.2.5. Antipyretic Medication 111
8.2.3. Phase 1 Stopping Rules 111
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 113
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 113
8.2.6. Pregnancy Testing 114
8.3. Adverse Events and Serious Adverse Events 114
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 114
8.3.1.1. Reporting SAEs to Pfizer Safety 116
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 116
8.3.2. Method of Detecting AEs and SAEs 116
8.3.3. Follow-up of AEs and SAEs 116
8.3.4. Regulatory Reporting Requirements for SAEs 117

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 117
8.3.5.1. Exposure During Pregnancy 117
8.3.6. Exposure During Breastfeeding 119
8.3.6.1. Occupational Exposure 119
8.3.7. Cardiovascular and Death Events 119
8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 120
8.3.9. Adverse Events of Special Interest 120
8.3.9.1. Lack of Efficacy 120
8.3.10. Medical Device Deficiencies 120
8.3.11. Medication Errors 120
8.4. Treatment of Overdose 121
8.5. Pharmacokinetics 122
8.6. Pharmacodynamics 122
8.7. Genetics 122
8.8. Biomarkers 122
8.9. Immunogenicity Assessments 122
8.10. Health Economics 122
8.11. Study Procedures 123
8.11.1. Phase 1 123
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 123
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 124
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 126
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 127
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 129
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 131
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 132
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 133

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)....134
8.11.1.10. Between Visits 8 and 9....134
8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2)....134
8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a)....136
8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a)....137
8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2....138
8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2....138
8.11.2. Phase 2/3....138
8.11.2.1. Visit 1 – Vaccination 1: (Day 1)....138
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)....141
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)....143
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)....144
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2....145
8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2....145
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction....146
8.13. COVID-19 Surveillance (All Participants)....147
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)....148
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)....149

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

8.14. Communication and Use of Technology 150
8.15. SARS-CoV-2 NAAT Results 150
8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo 151
8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2) 151
8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101) 153
8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102) 154
8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102) 154
8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102) 155
8.17. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) (Subset for Evaluation of Boostability and Protection Against Emerging VOCs) 155
8.17.1. Visit 301 – Vaccination 3: (150 to 210 Days After Visit 2) 156
8.17.2. Visit 302 – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 301) 158
8.17.3. Visit 303 – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 301) 159
8.17.4. Visit 304 – 1-Week Follow-up Visit (Vaccination 4): (6 to 8 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$ 160
8.17.5. Visit 305 – 1-Month Follow-up Visit (Vaccination 4): (28 to 35 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$ 161
8.17.6. Visit 306 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 301): 162
8.17.7. Visit 307 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 301): 162
8.18. Administration of BNT162b2$_{SA}$ to BNT162b2-naïve Participants 163
8.18.1. Visit 401 – Vaccination 1: (Day 1) 163
8.18.2. Visit 402 – Vaccination 2: (19 to 23 Days After Visit 401) 165
8.18.3. Visit 403 – 1-Week Follow-up Visit (After Vaccination 2): (6 to 8 Days After Visit 402) 167

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.18.4. Visit 404 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 402) 168
8.18.5. Visit 405 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 402) 168
8.18.6. Visit 406 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 402) 169
8.19. Surveillance for Asymptomatic SARS-CoV-2 Infection 169
8.19.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11 170
8.19.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection 171
8.20. Administration of a Third Dose of BNT162b2 to Participants Who Have Not Previously Received a Third Dose 171
8.20.1. Visit 501 – Third Dose of BNT162b2 172
8.20.2. Visit 502 – 1-Month Follow-up Telephone Contact: (28 to 35 Days After Visit 501) 173
8.20.3. Visit 503 – 6-Month Follow-up Telephone Contact: (175 to 189 Days After Visit 501) 174
8.20.4. Visit 504 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 501): 174
8.21. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis 175
9. STATISTICAL CONSIDERATIONS 175
9.1. Estimands and Statistical Hypotheses 175
9.1.1. Estimands 175
9.1.2. Statistical Hypotheses 176
9.1.2.1. Statistical Hypothesis Evaluation for Efficacy 176
9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity 176
9.2. Sample Size Determination 178
9.2.1. Phase 1 178
9.2.2. Efficacy Against COVID-19 178
9.2.3. Efficacy Against Asymptomatic Infection 179
9.2.4. Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years 179
9.2.5. Boostability and Protection Against Emerging SARS-CoV-2 VOCs 179

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

9.2.6. Safety 181
9.3. Analysis Sets 182
9.4. Statistical Analyses 184
9.4.1. Immunogenicity Analyses 184
9.4.2. Efficacy Analyses 194
9.4.3. Safety Analyses 200
9.4.4. Other Analyses 202
9.5. Interim Analyses 202
9.5.1. Analysis Timing 205
9.6. Data Monitoring Committee or Other Independent Oversight Committee 206
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 208
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 208
10.1.1. Regulatory and Ethical Considerations 208
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 208
10.1.2. Informed Consent Process 209
10.1.3. Data Protection 210
10.1.4. Dissemination of Clinical Study Data 210
10.1.5. Data Quality Assurance 211
10.1.6. Source Documents 213
10.1.7. Study and Site Start and Closure 213
10.1.8. Sponsor's Qualified Medical Personnel 214
10.2. Appendix 2: Clinical Laboratory Tests 215
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 217
10.3.1. Definition of AE 217
10.3.2. Definition of SAE 218
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 220
10.3.4. Reporting of SAEs 223
10.4. Appendix 4: Contraceptive Guidance 224
10.4.1. Male Participant Reproductive Inclusion Criteria 224

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

10.4.2. Female Participant Reproductive Inclusion Criteria....224
10.4.3. Woman of Childbearing Potential....225
10.4.4. Contraception Methods....226
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments....228
10.6. Appendix 6: Abbreviations....230
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19....234
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection....237
10.9. Appendix 9: Genetics....238
11. REFERENCES....239

LIST OF TABLES

Table 1. Local Reaction Grading Scale....109
Table 2. Systemic Event Grading Scale....110
Table 3. Scale for Fever....111
Table 4. Power Analysis for Noninferiority Assessment....179
Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes....181
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility....203
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses....204
Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall....204
Table 9. Laboratory Abnormality Grading Scale....215
Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)....235
Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)....236

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

LIST OF FIGURES

Figure 1. Multiplicity Schema.....178

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which continues to spread globally at high speed. To date, more than 215 million people have been infected with SARS-CoV-2 and >4 million have died, demonstrating an urgent need for efficacious vaccines.

Numerous COVID-19 vaccines are currently in development globally, and several candidate COVID-19 vaccines (eg, mRNA vaccines and adenovirus-vectored vaccines expressing the S protein) have been shown to be efficacious in the prevention of COVID-19 in clinical studies and are now available under temporary or emergency authorizations. BNT162b2, an RNA-based COVID-19 vaccine given as a 2-dose series administered 21 days apart, was shown to be safe and effective in a Phase 1/2/3 study and has received authorizations for temporary or emergency use or marketing authorizations in multiple countries and has been fully licensed for use in individuals 16 years of age and above in the US as of 23 Aug 2021.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 3 antigens:

BNT162b1 (variant RBP020.3): a modRNA encoding the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5);

BNT162b2 (variant RBP020.2): a modRNA encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9);

BNT162b2s01 (variant RBP020.11): a modRNA encoding the P2 S containing South Africa B.1.351 variant–specific mutations, hereafter referred to as BNT162b2$_{SA}$, as a representative variant of concern (VOC).

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and/or efficacy of these prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	• GMCs/GMTs at the time of Dose 3 and 7 days and 1 month after Dose 3. • GMFRs from before Dose 3 to 7 days and 1 month after Dose 3 • GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2 • GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2.	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
are expected.

Objectives[a]	Estimands	Endpoints
To describe the safety and tolerability profile of BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants, or as 2 doses to BNT162b2-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 5 or 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2 given as a third dose at least 6 months after the second dose of BNT162b2 (or BNT162b2$_{SA}$) for participants who received a third dose as part of protocol amendment 18	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • AEs from Dose 3 to 1 month after Dose 3 • SAEs from Dose 3 to 6 months after Dose 3	• AEs • SAEs
Primary Immunogenicity ***BNT162b2-experienced participants***		
To demonstrate the noninferiority of the anti–reference strain immune response after a third dose of BNT162b2 at 30 µg compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate the noninferiority of the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
BNT162b2-experienced participants		
To demonstrate the noninferiority of the anti-SA immune response after a third dose of BNT162b2 at 30 µg compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti–reference strain immune response after 1 dose of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ and a third dose of BNT162b2 at 30 µg	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg	SARS-CoV-2 SA NT in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$ or the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
To descriptively compare the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ and the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate a statistically greater anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 SA NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
To descriptively compare the anti–reference strain immune response after 2 doses of BNT162b2$_{SA}$ and after 2 doses of BNT162b2	GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period prior to receiving the third dose of BNT162b2 in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 after receiving the third dose of BNT162b2	In participants who received the third dose of BNT162b2: Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization	In participants who received BNT162b2 at initial randomization: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate and characterize the SARS-CoV-2 isolate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers • Identification of SARS-CoV-2 variant(s)
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers
To describe the immune response to any VOCs not already specified	Geometric mean NT for any VOCs not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2	• SARS-CoV-2 NTs for any VOCs not already specified
To describe the immune response to a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$	• GMTs at Dose 3 and subsequent time points • GMFRs from Dose 3 to subsequent time points	• SARS-CoV-2 reference strain NTs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and SA in a subset of participants: • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 2 doses to BNT162b2-naïve participants • 7 Days and 1 and 6 months after BNT162b2 given as a third dose to BNT162b2-experienced participants		

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for a description of the manufacturing process.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype $BNT162b2_{VOC}$ at 30 µg (based upon the South African variant and hereafter referred to as $BNT162b2_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive $BNT162b2_{SA}$ given as a 2-dose series, separated by 21 days.

As part of protocol amendment 18, to reflect current and anticipated recommendations for COVID-19 vaccine boosters, participants in C4591001 who meet specified recommendations (detailed separately and available in the electronic study portal) and have not already received one, will be offered a third dose of BNT162b2 after their second dose of BNT162. This opportunity is only for those participants who received their first 2 doses of BNT162 (including BNT162b1, BNT162b2, or $BNT162b2_{SA}$) as part of the study.

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

For evaluation of boostability and protection against emerging VOCs, 600 existing Phase 3 participants 18 to 55 years of age will be rerandomized in a 1:1 ratio to receive either a third dose of BNT162b2 at 30 µg or a third dose of BNT162b2$_{SA}$.

An additional group of 30 existing Phase 3 participants 18 to 55 years of age will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$. For these 30 participants, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the investigator and sponsor will not be. Serum samples from these participants may be used for assay development purposes and, except for objectives relating to response to a fourth dose, their results will be analyzed separately from the main immunogenicity analyses.

A further group of approximately 144 existing Phase 3 participants 18 years of age and older will be enrolled to receive a third, lower, dose of BNT162b2 of either 5 or 10 µg. Approximately 24 participants 18 to 55 years of age and 48 participants >55 years of age will be enrolled in each dose group.

Three hundred participants 18 to 55 years of age who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19 will be enrolled as a new cohort of participants to receive BNT162b2$_{SA}$ given as a 2-dose series.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 5 µg, 10 µg, 20 µg, 30 µg
- BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S containing South Africa B.1.351 variant–specific mutations): 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162.

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated. VE will be demonstrated if the lower bound of the 95% CI for VE is >20%.

In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

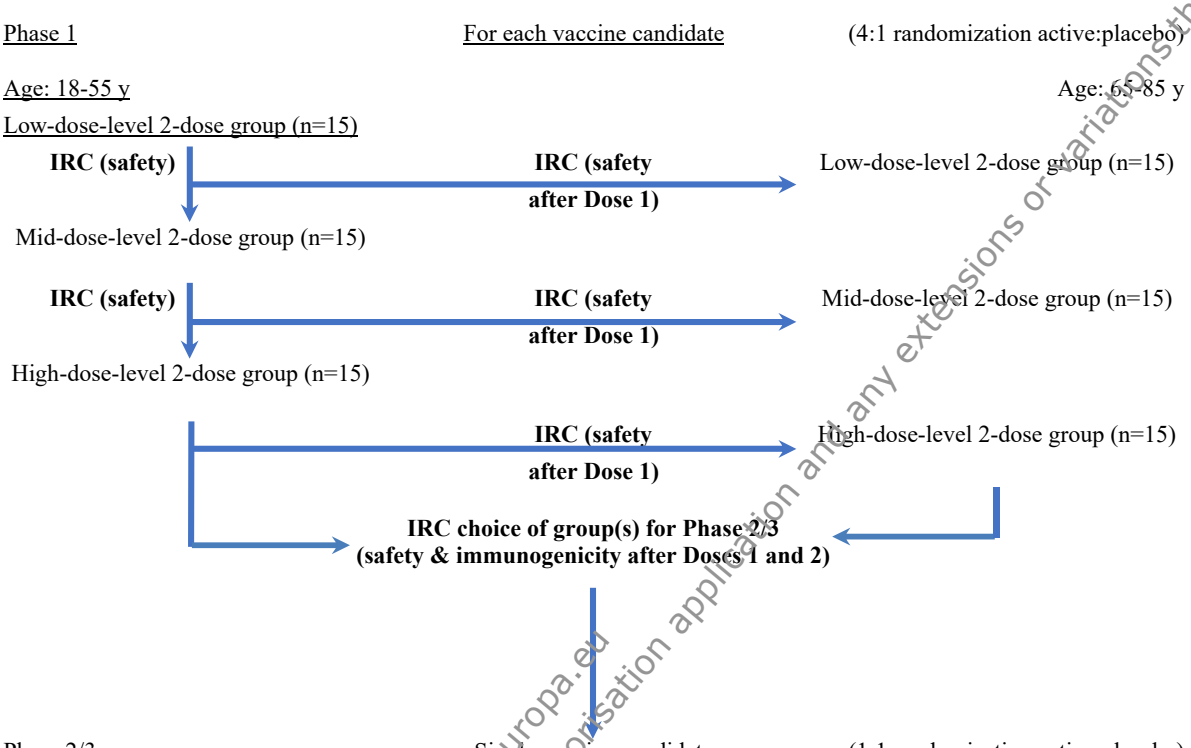
The boostability and protection against emerging VOCs for BNT162b2-experienced participants and BNT162b2-naïve participants will be assessed based on GMRs of SARS-CoV-2 SA-neutralizing and/or reference strain–neutralizing titers using a 1.5-fold noninferiority margin and the difference in percentages of participants with seroresponse using a 10% noninferiority margin.

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

Except for the objectives to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age and evaluation of boostability and protection against emerging VOCs by BNT162b2 and BNT162b2$_{SA}$ in Phase 3, the other immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMR, and the associated 95% CIs, for SARS-CoV-2 neutralizing titers, full-length S-binding or S1-binding IgG levels, and/or RBD-binding IgG levels (Phase 1 only) at the various time points.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

1.2. Schema



Abbreviation: IRC = internal review committee.

Note: Participants who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

1.3. Schedule of Activities

The SoA tables provide an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit is required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected. Prior to protocol amendment 16, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b1 or BNT162b2 (at any dose level) will continue in the study as originally planned.

All other participants will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study no later than at the approximate time participants in Phase 2/3 reach Visit 4. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain informed consent	X								*Continued on table below*	
Assign participant number	X									
Obtain demography and medical history data	X									
Obtain details of medications currently taken	X									
Perform physical examination	X	X	X	X	X	X	X			
Measure vital signs (including body temperature)	X	X	X	X	X	X	X			
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL				
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL									
Serological test for prior COVID-19 infection	~20 mL									
Perform urine pregnancy test (if appropriate)	X	X			X					
Obtain nasal (midturbinate) swab(s)[c]		X			X					X
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X		
Confirm eligibility	X	X			X					
Collect prohibited medication use			X	X	X	X	X	X		X

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Review hematology and chemistry results		X		X	X	X	X		*Continued on table below*	
Review temporary delay criteria		X			X					
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X		
Obtain randomization number and study intervention allocation		X								
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL		
Administer study intervention		X			X					
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X								
Provide thermometer and measuring device		X			X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►	◄	———	►			

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7		Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	***Study procedures for Visit 8 onwards continue on the next table***	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X		*Continued on table below*	
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X		X
Collect e-diary or assist the participant to delete application										
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)										X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who do not transition from placebo to BNT162b2)**		
Obtain informed consent		X					
Confirm participant originally received 10 to 30 µg of BNT162b1 or BNT162b2		X					
Perform urine pregnancy test (if appropriate)		X					
Confirm use of contraceptives (if appropriate)		X	X	X			
Collect prohibited medication use	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X			
Measure body temperature		X					
Confirm eligibility		X					
Review temporary delay criteria		X					
Collect blood sample for immunogenicity assessment	~20 mL	~20 mL	~20 mL	~20 mL	~20 mL	~20 mL	
Obtain nasal (midturbinate) swab(s)		X					X

This document cannot be used to support any marketing authorisation application. ema.europa.eu/ Any extensions or variations thereof

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who do not transition from placebo to BNT162b2)**		
Obtain the participant's vaccine vial allocation using the IRT system		X					
Administer 30-µg dose of BNT162b2		X					
Assess acute reactions for at least 30 minutes after study intervention administration		X					
Provide thermometer and measuring device		X					
Remind participant of e-diary technologies		X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		←	→				

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application
ema.europa.eu
Any extensions or variations thereof

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who do not transition from placebo to BNT162b2)**		
Review ongoing reactogenicity e-diary symptoms and obtain stop dates				X			
Collect AEs and SAEs as appropriate	X	X	X	X	X[b]	X[b]	X
Collect e-diary or assist the participant to delete application						X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: IRT = interactive response technology; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application or extensions or variations thereof
ema.europa.eu

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit is required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C. Prior to protocol amendment 16, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b2 or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b2 will continue in the study as originally planned.

All other participants who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4). If they want to receive BNT162b2, they will be unblinded and those who did originally receive placebo will move to the SoA in Section 1.3.3 for their remaining visits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Obtain informed consent	X						
Assign participant number	X						
Obtain demography and medical history data	X						
Perform clinical assessment[c]	X						
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X	
Measure height and weight	X						
Measure temperature (body)	X	X					
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X	X				
Collect nonstudy vaccine information	X	X	X	X			
Collect prohibited medication use		X	X	X	X	X	X
Confirm eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	
Obtain nasal (midturbinate) swab	X	X					X
Obtain randomization number and study intervention allocation	X						
Administer study intervention	X	X					

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X						
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	←	←					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X				
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X
According to eligibility, ascertain willingness to receive BNT162b2 if originally received placebo; if willing, unblind the participant's study intervention assignment (if not already done), and move placebo recipients to the SoA in Section 1.3.3			X	← X			
Collect e-diary or assist the participant to delete application						X	

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. Any placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2.

Visit Number	101	102	103	104	105	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Confirm participant meets local/national recommending criteria or is at least 175 days after Vaccination 2 (Visit 4/Visit 2)	X					
Obtain informed consent	X					
Confirm participant originally received placebo	X					
Perform urine pregnancy test (if appropriate)	X	X				
Confirm use of contraceptives (if appropriate)	X	X				
Collect prohibited medication use	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	
Review and consider eligibility	X	X				
Review temporary delay criteria	X	X				
Collect blood sample for immunogenicity assessment[c]	~20 mL					
Obtain nasal (midturbinate) swab	X	X				X
Obtain vaccine vial allocation via IRT	X	X				
Administer BNT162b2	X	X				
Assess acute reactions for at least 30 minutes after study intervention administration	X	X				

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Visit Number	101	102	103	104	105	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Collect AEs and SAEs as appropriate	X	X	X	X		X[d]
Contact the participant by telephone			X	X	X	
Request the participant return the e-diary or assist the participant to delete the application					X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)						X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

a. For participants who become eligible according to recommendations detailed separately and available in the electronic study reference portal.
b. For any remaining Phase 2/3 placebo recipients who wish to receive BNT162b2; may be combined with Visit 4 for Phase 2/3 participants.
c. Only if the participant has no blood sample collected in the previous 7 days.
d. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.4. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) (Subset for Evaluation of Boostability and Protection Against Emerging VOCs)

Select participants in Phase 3 at select sites who originally received 2 doses of BNT162b2 will be offered the opportunity to receive a third (and potentially fourth) dose of BNT162b2 or BNT162b2$_{SA}$.

Visit Number	301	302	303	304	305	306	307	Unplanned
Visit Description	Vax 3[a]	1-Week Follow-up Visit (After Vax 3)	1-Month Follow-up Visit (After Vax 3)	1-Week Follow-up Visit (After Vax 4)[b]	1-Month Follow-up Visit (After Vax 4)[b]	6-Month Follow-up Visit	18-Month Follow-up Visit	Potential COVID-19 Illness Visit[c]
Visit Window (Days)	150 to 210 Days After Visit 2	6 to 8 Days After Visit 301	28 to 35 Days After Visit 301	6 to 8 Days After Visit 303	28 to 35 Days After Visit 303	175 to 189 Days After Visit 301	532 to 560 Days After Visit 301	Optimally Within 3 Days After Potential COVID-19 Illness Onset
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4				
Obtain informed consent	X							
Confirm participant originally received BNT162b2 at Dose 1 and Dose 2	X							
Perform urine pregnancy test (if appropriate)	X		X[b]					
Confirm use of contraceptives (if appropriate)	X	X	X	X	X			
Collect prohibited medication use	X	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X	X	X		
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X			X	X	
Measure body temperature	X		X[b]					
Confirm eligibility	X		X[b]					
Review temporary delay criteria	X		X[b]					

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Visit Number	301	302	303	304	305	306	307	Unplanned
Visit Description	**Vax 3[a]**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**1-Week Follow-up Visit (After Vax 4)[b]**	**1-Month Follow-up Visit (After Vax 4)[b]**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**150 to 210 Days After Visit 2**	**6 to 8 Days After Visit 301**	**28 to 35 Days After Visit 301**	**6 to 8 Days After Visit 303**	**28 to 35 Days After Visit 303**	**175 to 189 Days After Visit 301**	**532 to 560 Days After Visit 301**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			**ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4**				
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation[d]	~120 mL	~120 mL	~120 mL			~120 mL		
Collect blood sample for HLA typing[d]	~5 mL							
Obtain nasal (midturbinate) swab(s)	X		X[b]					X
Obtain randomization number and study intervention allocation using the IRT system	X							
Administer study intervention	X		X[b]					
Assess acute reactions for at least 30 minutes after study intervention administration	X		X[b]					
Provide thermometer and measuring device	X							
Remind participant of e-diary technologies	X		X[b]					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	←	→		↔				

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	301	302	303	304	305	306	307	Unplanned
Visit Description	Vax 3[a]	1-Week Follow-up Visit (After Vax 3)	1-Month Follow-up Visit (After Vax 3)	1-Week Follow-up Visit (After Vax 4)[b]	1-Month Follow-up Visit (After Vax 4)[b]	6-Month Follow-up Visit	18-Month Follow-up Visit	Potential COVID-19 Illness Visit[c]
Visit Window (Days)	150 to 210 Days After Visit 2	6 to 8 Days After Visit 301	28 to 35 Days After Visit 301	6 to 8 Days After Visit 303	28 to 35 Days After Visit 303	175 to 189 Days After Visit 301	532 to 560 Days After Visit 301	Optimally Within 3 Days After Potential COVID-19 Illness Onset
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4				
Review ongoing reactogenicity e-diary symptoms and obtain stop dates			X		X			
Collect AEs and SAEs as appropriate	X	X	X	X	X	X[e]	X[e]	X
Collect e-diary or assist the participant to delete application							X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)								X

Abbreviations: e-diary = electronic diary; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; vax = vaccination.

a. Visit 301 can occur on the same day as Visit 4, but all procedures for both visits must be conducted (including collection of all blood samples).
b. Only for those participants who will receive Dose 4.
c. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
d. Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants who will receive a third (but not fourth) dose of BNT162b2 at 30 µg or $BNT162b2_{SA}$ at select sites only.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.5. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants

As part of Amendment 14, an additional cohort of BNT162b2-naïve participants will be enrolled to receive BNT162b2$_{SA}$ per the following SoA.

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain informed consent	X						
Assign participant number	X						
Obtain demography and medical history data	X						
Perform clinical assessment[c]	X						
Measure height and weight	X						
Measure temperature (body)	X	X					
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X	X	X			
Collect nonstudy vaccine information	X	X	X	X	X		
Collect prohibited medication use		X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X			X	X	X	
Confirm eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment	~50 mL		~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation[d]	~120 mL		~120 mL	~120 mL	~120 mL		
Collect blood sample for HLA typing[d]	~5 mL						

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain nasal (midturbinate) swab	X	X					X
Obtain the participant's vaccine vial allocation using the IRT system	X	X					
Administer BNT162b2$_{SA}$	X	X					
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X						
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	◄—►	◄—►					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X		X			
Collect AEs and SAEs as appropriate	X	X	X	X	X[e]	X[e]	X
Collect e-diary or assist the participant to delete application						X	

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: e-diary = electronic diary; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; vax = vaccination.

a. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
b. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
c. Including, if indicated, a physical examination.
d. Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants at select sites only.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

1.3.6. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4 or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

Visit Number	201	202 Onward
Visit Description	**Asymptomatic SARS-CoV-2 Infection Surveillance Consent**	**Asymptomatic SARS-CoV-2 Infection Surveillance Swab**
Visit Window (Days)	**From Approval of Protocol Amendment 11**	**Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection**
Obtain informed consent for asymptomatic SARS-CoV-2 infection surveillance	X	
Collect prohibited medication use	X	
Collect blood sample for immunogenicity assessment[a]	~20 mL/~10 mL	
Obtain nasal (midturbinate) swab (self-swab at home or by site staff at an in-person visit)	X	X
Collect AEs and SAEs as appropriate[b]	X	

a. Only if the participant has no blood sample collected in the previous 7 days. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
b. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

1.3.7. Administration of a Third Dose of BNT162b2 to Participants Who Have Not Previously Received a Third Dose

As part of protocol amendment 18, to reflect current and anticipated recommendations for COVID-19 vaccine boosters, participants in C4591001 who have not already received one, will be offered a third dose of BNT162b2 from at least 6 months (175 days) after their second dose of BNT162. The opportunity to receive a third dose of BNT162b2 will be offered as part of the study, according to recommendations detailed separately, and available in the electronic study reference portal. This opportunity is only for those participants who received their first 2 doses of BNT162 (including BNT162b1, BNT162b2, or BNT162b2$_{SA}$) as part of the study.

Once a participant receives a vaccination at Visit 501, all remaining study visits will follow the SoA as set out below.

The additional information collected at Visits 501, 502, 503, and 504 will be collected in a supplementary database; further information on the recording of this information will be provided in the study CRF Completion Requirements document.

Visit Number	501	502	503	504	Unplanned
Visit Description	**Third Dose of BNT162b2**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**12-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Per Recommendation[a]**	**28 to 35 Days After Visit 501**	**175 to 189 Days After Visit 501**	**350 to 378 Days After Visit 501**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Confirm participant has only received 2 doses of BNT162 as part of the study and not outside the study	X				
Obtain informed consent	X				
Perform urine pregnancy test (if appropriate)	X				
Confirm use of contraceptives (if appropriate)	X				
Collect nonstudy vaccine information	X	X	X		
Collect prohibited medication use[b]	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X	X	X	X	
Review and consider eligibility	X				
Review temporary delay criteria	X				
Collect blood sample for immunogenicity assessment	~20 mL			~20 mL	
Obtain nasal (midturbinate) swab	X				X
Obtain vaccine vial allocation via IRT	X				

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Visit Number	501	502	503	504	Unplanned
Visit Description	**Third Dose of BNT162b2**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**12-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Per Recommendation[a]**	**28 to 35 Days After Visit 501**	**175 to 189 Days After Visit 501**	**350 to 378 Days After Visit 501**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Administer BNT162b2	X				
Assess acute reactions for at least 30 minutes after study intervention administration	X				
Collect AEs and SAEs as appropriate[b]	X	X	X		X[c]
Contact the participant by telephone		X	X		
Request the participant return the e-diary device or assist the participant to delete the application				X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)					X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

a. The opportunity to receive a third dose of BNT162b2 will be offered as part of the study, according to recommendations detailed separately, and available in the electronic study reference portal.
b. AEs, nonstudy prohibited medications, and information relating to a potential COVID-19 illness will still be recorded in the original study database.
c. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. To-date, more than 215 million people have been infected with SARS-CoV-2 and >4 million have died, demonstrating an urgent need for efficacious vaccines.[3]

Numerous COVID-19 vaccines are currently in development globally, and several candidate COVID-19 vaccines (eg, mRNA vaccines and adenovirus-vectored vaccines expressing the S protein) have been shown to be efficacious in the prevention of COVID-19 in clinical studies and are now available under temporary or emergency authorizations. BNT162b2, an RNA-based COVID-19 vaccine given as a 2-dose series administered 21 days apart, was shown to be safe and effective in a Phase 1/2/3 study and has received authorizations for temporary or emergency use or marketing authorizations in multiple countries and has been fully licensed for use in individuals 16 years of age and above in the US as of 23 Aug 2021.

As more data about COVID-19 continue to accrue, the potential duration of protection afforded after a wild-type SARS-CoV-2 infection, and by vaccination, remains unknown. In addition, mutated SARS-CoV-2 VOCs have started to emerge, for example in the UK

(known as 20I/501Y.V1, VOC 202012/01, or B.1.1.7), SA (known as 20H/501Y.V2 or B.1.351), and Brazil (known as P.1).[4]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[5,6]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Three SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 3 antigens:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5);
- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9);
- **BNT162b2s01** (variant RBP020.11): nucleoside-modified messenger RNA (modRNA) as above, but encoding the P2 S containing South Africa B.1.351 variant–specific mutations, hereafter referred to as BNT162b2$_{SA}$, as a representative variant of concern (VOC).

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

In light of the unknowns regarding duration of protection, as well as the emerging VOCs, it is important to understand the boostability of BNT162, and potential heterologous protection against emerging VOC(s). A first step to address this will be to study an additional dose of BNT162b2 at 30 µg given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ (based upon the South African variant and hereafter referred to as

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof are not proposed.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

BNT162b2$_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

As part of protocol amendment 18, to reflect current and anticipated recommendations for COVID-19 vaccine boosters, participants in C4591001 who meet specified recommendations and have not already received one, will be offered a third dose of BNT162b2 after their second dose of BNT162b1, BNT162b2 or BNT162b2$_{SA}$. The opportunity to receive a third dose of BNT162b2 will be offered as part of the study, according to recommendations detailed separately, and available in the electronic study reference portal.

2.3. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[7] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[8] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.4. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with the currently available therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.

- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.

- All participants 12 to 15 years of age will be included in the reactogenicity subset (see Section 8.2.2).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

2.4.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[9]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.
Very rare cases of anaphylaxis, myocarditis, and pericarditis have been reported after authorization in recipients of BNT162b2.	Anaphylaxis: The estimated rate is 5.0 per million doses administered. Myocarditis and pericarditis: Very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. These are generally mild cases, and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.	Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 8.2.1.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

2.4.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of an efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.4.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	• GMCs/GMTs at the time of Dose 3 and 7 days and 1 month after Dose 3. • GMFRs from before Dose 3 to 7 days and 1 month after Dose 3	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels
	• GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers
	• GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives	Estimands	Endpoints
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants, or as 2 doses to BNT162b2-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 5 or 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2 given as a third dose at least 6 months after the second dose of BNT162b2 (or BNT162b2$_{SA}$) for participants who received a third dose as part of protocol amendment 18	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • AEs from Dose 3 to 1 month after Dose 3 • SAEs from Dose 3 to 6 months after Dose 3	• AEs • SAEs
Primary Immunogenicity ***BNT162b2-experienced participants***		
To demonstrate the noninferiority of the anti–reference strain immune response after a third dose of BNT162b2 at 30 µg compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Objectives[a]	Estimands	Endpoints
BNT162b2-naïve participants		
To demonstrate the noninferiority of the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
BNT162b2-experienced participants		
To demonstrate the noninferiority of the anti-SA immune response after a third dose of BNT162b2 at 30 µg compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Objectives[a]	Estimands	Endpoints
To demonstrate the noninferiority of the anti–reference strain immune response after 1 dose of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ and a third dose of BNT162b2 at 30 µg	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg	SARS-CoV-2 SA NT in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$ or the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ and the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate a statistically greater anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 SA NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
To descriptively compare the anti–reference strain immune response after 2 doses of BNT162b2$_{SA}$ and after 2 doses of BNT162b2	GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Objectives[a]	Estimands	Endpoints
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period prior to receiving the third dose of BNT162b2 in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 after receiving the third dose of BNT162b2	In participants who received the third dose of BNT162b2: Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization	In participants who received BNT162b2 at initial randomization: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate and characterize the SARS-CoV-2 isolate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers • Identification of SARS-CoV-2 variant(s)
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers
To describe the immune response to any VOCs not already specified	Geometric mean NT for any VOCs not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2	• SARS-CoV-2 NTs for any VOCs not already specified
To describe the immune response to a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$	• GMTs at Dose 3 and subsequent time points • GMFRs from Dose 3 to subsequent time points	• SARS-CoV-2 reference strain NTs
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and SA in a subset of participants: • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 2 doses to BNT162b2-naïve participants • 7 Days and 1 and 6 months after BNT162b2 given as a third dose to BNT162b2-experienced participants		

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for description of the manufacturing process.

Up until the final efficacy analysis, this protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ at 30 µg (based upon the South African variant and hereafter referred to as

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

BNT162b2$_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than at the approximate time participants in Phase 2/3 reach Visit 4.

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162.

Participants are expected to participate for up to a maximum of approximately 26 months.

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 280 participants from each of the 2 age groups (12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

For evaluation of boostability and protection against emerging VOCs, 600 existing Phase 3 participants 18 to 55 years of age will be rerandomized in a 1:1 ratio to receive either a third dose of BNT162b2 at 30 µg or a third dose of BNT162b2$_{SA}$.

A further group of approximately 144 existing Phase 3 participants 18 years of age and older will be enrolled to receive a third, lower, dose of BNT162b2 of either 5 or 10 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Approximately 24 participants 18 to 55 years of age and 48 participants >55 years of age will be enrolled in each dose group. An additional group of 30 existing Phase 3 participants 18 to 55 years of age will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$. For these 30 participants, through 1 month after their first dose of BNT162b2$_{SA}$ the participant will be blinded to their vaccine allocation but the investigator and Sponsor will not be. Serum samples from these participants may be used for assay development purposes and, except for objectives relating to response to a fourth dose, their results will be analyzed separately from the main immunogenicity analyses.

Three hundred participants 18 to 55 years of age who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19 will be enrolled as a new cohort of participants to receive BNT162b2$_{SA}$ given as a 2-dose series.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 2/3 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4).

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

The changes to the protocol as part of protocol amendment 14 to assess boostability and homologous/heterologous protection against emerging VOCs allow the evaluation of safety and immunogenicity of BNT162b2$_{SA}$:

- When given as a third dose to C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously (ie, BNT162b2-experienced) and have not experienced COVID-19.
- In a small separate group of individuals who previously received 2 doses of BNT162b2 followed by 1 dose of BNT162b2$_{SA}$, a second BNT162b2$_{SA}$ dose will also be given 1 month after Dose 1 of BNT162b2$_{SA}$.
- When given as a 2-dose series, separated by 21 days, in newly recruited participants who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

In addition, a group of C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously will receive a third dose of BNT162b2.

This approach will allow an evaluation of immunogenicity against the reference ancestral SARS-CoV-2 strain (Wuhan-Hu-1/USA-WA1) and the selected South African VOC using a noninferiority approach based on neutralizing antibody titers in prior BNT162b2 vaccinees who receive either a homologous boost (with BNT162b2) or a heterologous boost (with BNT162b2$_{SA}$), as well as new vaccinees receiving 2 doses of BNT162b2$_{SA}$.

As part of protocol amendment 18, to reflect current and anticipated recommendations for COVID-19 vaccine boosters, participants in C4591001 who meet specified recommendations (detailed separately and available in the electronic study portal) and have not already received one, will be offered a third dose of BNT162b2 after their second dose of BNT162. The opportunity to receive a third dose of BNT162b2 will be offered as part of the study, according to recommendations detailed separately, and available in the electronic study reference portal. This opportunity is only for those participants who received their first 2 doses of BNT162 (including BNT162b1, BNT162b2, or BNT162b2$_{SA}$) as part of the study.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.6. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness visit will occur and, prior to protocol amendment 16, a subsequent convalescent visit would occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization.

   For the boostability and protection-against-VOCs subset:

   - Existing participants enrolled to receive a third dose of BNT162b2 at 30 µg or BNT162b2$_{SA}$, male or female participants between the ages of 18 and 55 years, inclusive, at rerandomization.
   - Newly enrolled participants enrolled to receive 2 doses of BNT162b2$_{SA}$; male or female participants between the ages of 18 and 55 years, inclusive, at enrollment.
   - Existing participants enrolled to receive a third dose of BNT162b2 at 5 or 10 µg; male or female participants ≥18 years at rerandomization.

   Note that participants <18 years of age cannot be enrolled in the EU.

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

5. **Boostability and protection-against-VOCs existing participant subset only:** Participants who provided a serum sample at Visit 3, with Visit 3 occurring within the protocol-specified window.

Informed Consent:

6. Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

5. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - Chronic liver disease
    - Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
    - Resident in a long-term facility
    - BMI >30 kg/m^2
    - Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry through and including 28 days after the last dose of study intervention, with the exception of non-Pfizer interventional studies for prevention of COVID-19, which are prohibited throughout study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Other Exclusions:

22. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:

    - New or increased cough;
    - New or increased shortness of breath;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

2. Receipt of any seasonal or pandemic influenza vaccine within 14 days (not applicable for the third dose of BNT162b2 at Visit 501), or any other nonstudy vaccine within 28 days, before study intervention administration.

3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days (not applicable for the third dose of BNT162b2 at Visit 501), or any other nonstudy vaccine within 28 days, after study intervention administration.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 3 investigational RNA vaccine candidates, with the addition of saline placebo, are the 4 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 5 µg, 10 µg, 20 µg, 30 µg
- BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S containing South Africa B.1.351 variant–specific mutations): 30 µg

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	5-, 10-, 20-, 30-µg	30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. Participants who originally received placebo and accept the offer to receive BNT162b2 at defined points as part of the study will receive 1 dose of BNT162b2 at each additional vaccination visit (Visits 101 and 102) in accordance with the study's additional SoA (Section 1.3.3). The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162 at Visit 8a.

Participants in the subset for evaluation of boostability and protection against emerging VOCs will receive either a third dose of BNT162b2 or BNT162b2$_{SA}$ approximately 5 to 7 months after their second dose of BNT162 at Visit 301. Of those who receive BNT162b2$_{SA}$ at Visit 301, a subset will receive a further dose of BNT162b2$_{SA}$ at Visit 303.

BNT162b2-naïve participants who are enrolled under protocol amendment 14 to receive BNT162b2$_{SA}$ will receive 1 dose of study intervention at each vaccination visit, Visits 401 and 402.

As part of protocol amendment 18, participants who have not yet received a third dose of BNT162b2 may receive one at Visit 501, at least 6 months (175 days) after their second dose of BNT162. The administration of a third dose of BNT162b2 at Visit 501 will be conducted in an open-label manner; therefore, the requirement for an unblinded dispenser/administrator does not apply to this vaccination.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

9. Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

To allow administration of BNT162b2 to participants who originally received placebo, site staff will be unblinded to individual participants' original study intervention allocation as the participants become eligible for vaccination under local/national recommendations or from 6 months after the second dose.

For the group of 30 existing Phase 3 participants 18 to 55 years of age who will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the investigator will not be.

The administration of a third dose of BNT162b2 at Visit 501 will be conducted in an open-label manner.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).

- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document can not be used to support any marketing authorisation application and any extensions or variations thereof www.ema.europa.eu

- After the formal data release of the final efficacy analysis of at least 164 cases, which is considered the primary completion of the study efficacy objectives, additional statisticians and programmers will become unblinded at the participant level to prepare unblinded analyses and other regulatory activities. A group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study.

- After the study data used for submission become public, the blinded study team will also have access to those data, and become unblinded at a group level.

- When a participant is unblinded for potential receipt of BNT162b2 (if he or she originally received placebo) per Section 8.16, the study team will become unblinded to the participant's original study intervention allocation.

For the group of 30 existing Phase 3 participants 18 to 55 years of age who will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the sponsor will not be.

The study will be unblinded in stages once all ongoing participants either have been individually unblinded or have concluded their 6-month post–Dose 2 or post–Dose 3 study visit, as follows:

- Phase 1 (after Visit 8).

- Phase 2/3, ≥16 years (after Visit 4).

- Phase 3, 12 to 15 years (after Visit 4).

- Original Phase 3 participants rerandomized to assess boostability and protection against emerging VOCs (after Visit 306).

The administration of a third dose of BNT162b2 at Visit 501 will be conducted in an open-label manner.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

Instructions on how to unblind participants ahead of administration of BNT162b2 to placebo recipients, or for other, nonemergency reasons, will be provided separately: this unblinding will NOT be performed in the IRT. The date (that the participant becomes aware of study intervention allocation) and reason that the blind was broken must be recorded in the source documentation and CRF.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants). In addition, for Phase 1 participants who go on to receive a third dose of BNT162, concomitant vaccinations will be collected from the time the participant provides informed consent (for receipt of vaccination 3) through and including Visit 8c (1 month after the third dose). For BNT162-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to the time the participant provides informed consent (for participation in the subset) through and including Visit 306. For BNT162b2-naïve participants, the subset for evaluation of protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to study enrollment through and including Visit 405. For participants who receive a third dose of BNT162b2 at Visit 501, all vaccinations received will be recorded from 28 days prior to the time the participant provides informed consent (for receipt of the third dose) through Visit 503.
    - Nonstudy coronavirus vaccines are listed in Section 6.5.1 as prohibited throughout the study and should therefore be recorded at any time they are given during study participation. This includes blinded BNT162b2 vaccine/placebo given in the B7471026 study.
- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.
- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention. For participants receiving the third dose of BNT162b2 at Visit 501, the administration of the seasonal and pandemic influenza vaccine is not prohibited.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 and from 28 days prior to Visit 8a to Visit 8c for Phase 1 participants, and from 28 days prior to enrollment to Visit 3 for Phase 2/3 participants). Use is also prohibited for participants in the subset for evaluation of boostability and protection against emerging VOCs, from 28 days prior to Visit 301 to Visit 303/305 and the BNT162b2-naïve participants from 28 days prior to enrollment to Visit 404.

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, for whatever reason, a participant receives only 1 dose of BNT162b2, the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. This opportunity also extends to the third dose of BNT162b2, in the event of an issue with the planned administration. For example, because of a medication error a participant receives only 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa); the participant can return at a later date for the unscheduled visit. In this situation:

- Obtain informed consent.
- Measure the participant's body temperature (only in the event the unscheduled visit is to administer a second, not third, dose).
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Unblinded or blinded (depending on time point in the study) site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s).

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Note: Participants who are randomized in the C4591031 or the BNT162-17 study should be withdrawn from this study.

From protocol amendment 18 onwards, participants who receive COVID-19 vaccines outside of the study should be withdrawn. This does not apply if the nonstudy COVID-19 vaccine was administered prior to site receipt of IRB/EC approval of protocol amendment 18.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

If a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, she/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately up to: 500 mL for participants in Phase 1, 150 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum.

Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 670 mL during the 24-month study period.

For those Phase 3 participants enrolled in the subset to receive an additional dose of BNT162b2 or BNT162b2$_{SA}$, the total blood sampling volume for individual participants in this study is approximately up to 310 mL for those who receive 3 doses and 410 mL for those who receive 4 doses. Those participants in the subset who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of approximately up to 795 mL.

For those participants enrolled into the additional cohort (added as part of protocol amendment 14) of BNT162b2-naïve participants who will receive 2 doses of BNT162b2$_{SA}$, the total blood sampling volume for individual participants is approximately up to 250 mL. Those participants in the cohort who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of approximately up to 735 mL.

For all participants, other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

8.1.1. Efficacy Against COVID-19

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[10] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA and Pfizer validated), or

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
  - Fever;
  - New or increased cough;
  - New or increased shortness of breath;
  - Chills;
  - New or increased muscle pain;
  - New loss of taste or smell;
  - Sore throat;
  - Diarrhea;
  - Vomiting.

  The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction*;
  - Admission to an ICU;
  - Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

8.1.2. Efficacy Against Asymptomatic SARS-CoV-2 Infection

VE against asymptomatic SARS-CoV-2 infection will be evaluated in 2 ways, through impact on seroconversion of N-binding antibody and impact on NAAT-confirmed SARS-CoV-2 infection, in originally enrolled Phase 2/3 participants not suffering from COVID-19. Data from participants who receive more than 2 doses of BNT162b2 will not be included after they receive a third dose.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

8.1.2.1. Seroconversion of N-Binding Antibody

Blood samples for assessment of N-binding antibodies are drawn at multiple scheduled visits. An asymptomatic case of SARS-CoV-2 infection based on seroconversion of N-binding antibody is defined as positive N-binding antibody at a post–Dose 2 visit in participants without serological evidence of infection (determined by negative N-binding antibody) at Visit 1 or virological evidence of infection (determined by negative NAAT result at Visit 1 and Visit 2, and at the time of a potential COVID-19 illness). The requirement for a negative NAAT result at Visit 2 is to focus on assessment of protection against asymptomatic infection after 2 doses of vaccine, to the extent possible in an analysis based on seroconversion of N-binding antibody, recognizing that it is not possible to identify and exclude all asymptomatic infections that occur after Dose 1 and prior to Dose 2.

A secondary definition will be applied without the requirement for a negative NAAT result at Visit 2 to allow assessment of protection after 1 dose of vaccine. A positive N-binding antibody at a postvaccination visit in participants with negative N-binding antibody at Visit 1 and negative NAAT results at Visit 1 and at the time of a potential COVID-19 illness is considered an asymptomatic case.

8.1.2.2. NAAT-Confirmed SARS-CoV-2 Infection

For participants who consent to participate in an intensive period of surveillance, nasal swabs will be obtained to assess SARS-CoV-2 infection by NAAT (see Section 8.1.5).

An asymptomatic case of NAAT-confirmed SARS-CoV-2 infection is defined as a positive NAAT result on a nasal swab collected during the surveillance period from participants without COVID-19 symptoms at the time the nasal swab was taken, or within 14 days after it. The onset date of the asymptomatic case is the collection date of the first nasal swab that tested positive.

8.1.3. Vaccine-Induced Immunogenicity

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay (reference strain and SA variant)
- Full-length S-binding or S1-binding IgG level assay
- RBD-binding IgG level assay (Phase 1 only)

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Additional whole blood samples of ~120 mL will be obtained from a group of up to approximately 30 participants in each 30-µg group in the subset for evaluation of boostability and protection against emerging VOCs (both BNT162b2-experienced and BNT162b2-naïve) at select sites for isolation of PBMCs. These samples will be used to describe T-cell responses to emerging VOCs and reference strains. Some of the sample may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs, for understanding the B-cell, T-cell, and antibody repertoires. A blood sample of ~5 mL for HLA typing will also be obtained. Some of the 5-mL blood sample collected for HLA typing may be used for DNA and/or RNA isolation to further characterize HLA type.

8.1.4. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine related assay work supporting vaccine programs. No testing of the participant's DNA will be performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

8.1.5. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.6.

The nasal swabs will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2. For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with Section 8.3.2.

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

This document cannot be used to support any marketing authorisation application from ema.europa.eu and any extensions or variations thereof

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Certain participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. In addition, participants 16 through 17 years of age enrolled under protocol amendment 9 and onwards will be included in the reactogenicity subset. All other participants, including those who originally received placebo and then received BNT162b2 under protocol amendment 10 and onwards, will not complete a reactogenicity e-diary but will have their local reactions and systemic events detected and reported as AEs in accordance with Section 8.3.2. Phase 1 participants who receive a third dose of BNT162b2 will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage in the reactogenicity e-diary for 7 days following administration of the study intervention. Participants in the subset for evaluation of boostability and protection against emerging VOCs (both BNT162b2-experienced and BNT162b2-naïve) will be asked to monitor and record local reactions, systemic events, and antipyretic medication use in the reactogenicity e-diary for 7 days following each administration of the study intervention.

The participants receiving a third dose of BNT162b2 at Visit 501 will not complete a reactogenicity e-diary following vaccination.

The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[9]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the administration of the second dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.
2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.
3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.
4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

Administration of BNT162b2 to pregnant participants at Visits 101 and 102 (participants who originally received placebo and choose to be unblinded and receive BNT162b2) or at Visit 501 may be considered if there are local or national recommendations for COVID-19 vaccination of pregnant women, and the investigator and participant are in agreement. This overrides the requirements stated in the previous paragraph, and will not be considered as a protocol deviation. However, the EDP should still be reported in accordance with Section 8.3.5.1.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Additionally, for those participants who originally received placebo but go on to receive BNT162b2 at Vaccinations 3 and 4, AEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) through and including Visit 103. SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) to approximately 6 months after the second dose of BNT162b2 (Visit 104).

For Phase 1 participants who go on to receive a third dose of BNT162, AEs and SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccination 3) through and including Visit 8c (1 month after the third dose).

For BNT162b2-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, AEs will be collected from the time the participant provides informed consent (for participation in the subset) through and including Visit 303 for those receiving 1 additional dose and Visit 305 for those who receive 2 additional doses. For both schedules, this equates to collection for up to 1 month after the last dose. SAEs will be collected from the time the participant provides informed consent (for participation in the subset) through and including Visit 306 (5 or 6 months after the last dose, depending upon group).

For BNT162b2-naïve participants, the subset for evaluation of protection against emerging VOCs, AEs will be collected from the time the participant provides informed consent through and including Visit 404 (1 month after the second dose). SAEs will be collected from the time the participant provides informed consent through and including Visit 405 (6 months after the second dose).

For participants who receive a third dose of BNT162b2 at Visit 501, AEs will be collected from the time the participant provides informed consent (for administration of the third dose of BNT162b2) through Visit 502 (1 month after the third dose of BNT162b2). SAEs will be collected from the time the participant provides informed consent (for administration of the third dose of BNT162b2) through Visit 503 (6 months after the third dose of BNT162b2).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
  - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose of study intervention. Beyond 28 days after the last dose of study intervention, any pregnancy that occurs will not be considered EDP for this study.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case by case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof in the European Union

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.6. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.6.1. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

8.3.7. Cardiovascular and Death Events

Not applicable.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document can not be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.9. Adverse Events of Special Interest

The following events are considered AESIs:

- A confirmed diagnosis of myocarditis or pericarditis. See Section 8.21 for additional procedures for monitoring of potential myocarditis or pericarditis.

8.3.9.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.10. Medical Device Deficiencies

Not applicable.

8.3.11. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Some of the blood samples collected for PBMC isolation and HLA typing may be used for DNA and/or RNA isolation. The DNA and/or RNA samples from the PBMC isolation may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs, for understanding the B-cell, T-cell, and antibody repertoires. The DNA and/or RNA samples from the blood sample for HLA typing may be used to further characterize HLA type.

See Appendix 9 for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

8.11. Study Procedures

Unless stated otherwise, all study visits are intended to be conducted in person at the study site. If this is not possible, because of local circumstances related to the COVID-19 pandemic, study procedures that do not require in-person participant contact may be performed by telehealth. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Irrespective of the nature of the contact, all visit procedures are expected to be performed on the same day.

As the protocol design includes visits of an unplanned nature, multiple visits may occur on the same day, but all procedures for all visits must be conducted (including collection of all blood samples).

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Fever ≥39.0°C (≥102.1°F).
- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Between Visits 8 and 9

All participants who have not already been unblinded, no later than at the approximate time participants in Phase 2/3 reach Visit 4, will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, he or she will move to the procedures in Section 8.16.

8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of a third dose of BNT162, his or her next visit should be Visit 9.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Confirm that the participant originally received 10-µg, 20-µg, or 30-µg doses of BNT162b1 or BNT162b2 at Vaccinations 1 and 2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Record nonstudy vaccinations as described in Section 6.5.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 2, 3, and 6 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer a 30-µg dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
    - Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):
  - Fever ≥39.0°C (≥102.1°F)
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)
  - Severe pain at the injection site
  - Any severe systemic event
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD must be personally dated

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Obtain a nasal (midturbinate) swab (collected by site staff).

- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.

    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

    - Fever ≥39.0°C (≥102.1°F).

    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).

- Measure the participant's body temperature.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Obtain a nasal (midturbinate) swab (collected by site staff).

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.

- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).

- Discuss contraceptive use as described in Section 10.4.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

- If Visit 3 is being conducted under amendment 12 onward: If the participant is eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, determine if he/she is willing to receive BNT162b2 as part of the study. If so, unblind the participant's study intervention assignment, and move placebo recipients to the procedures in Section 8.16.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.

- Record nonstudy vaccinations as described in Section 6.5.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.

- Schedule an appointment for the participant to return for the next study visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emea.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- If not already unblinded, unblind the participant's study intervention assignment, and move placebo recipients willing to receive BNT162b2 to the procedures in Section 8.16.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support and marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination (either as part of this study, co-enrolled C459 studies, or the B7471026 [20vPnC] study), potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
  - Symptoms and signs, including
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
    - Significant acute renal, hepatic, or neurologic dysfunction
    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)
  - Clinical diagnosis
  - Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.
  - Full blood count
  - Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
  - Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
  - Number and type of any healthcare contact; duration of hospitalization and ICU stay
  - Death
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

Prior to protocol amendment 16, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol; however, data collected

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

from convalescent visits that occurred prior to protocol amendment 16 will remain part of the study data set.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

8.15. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 or 14 days after receipt of the second dose, depending on the objective) of past SARS-CoV-2 infection.
- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Asymptomatic SARS-CoV-2 infection surveillance visits: To determine the incidence of asymptomatic SARS-CoV-2 infection.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, asymptomatic SARS-CoV-2 infection surveillance visit swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result, either asymptomatic or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result), prior to Visit 2 should receive Vaccination 2 as normal.

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

If a participant becomes eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study.

Placebo recipients who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Dose 2, and will follow the procedures listed in this section for the remainder of their participation in the study. For Phase 2/3 participants, Visit 101 could occur at the same time as the original Visit 4.

8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant originally received only placebo at Vaccination 1/2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 4 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101)

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Record AEs as described in Section 8.3.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record AEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 103 (if any).

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment to call the participant by telephone for the next study contact.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 104 (if any).

- Request the return of the participant's e-diary or assist the participant/participant's parent(s)/legal guardian to remove the study application from his or her own personal device.

- Inform the participant/participant's parent(s)/legal guardian that his or her study participation has ended.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.17. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) (Subset for Evaluation of Boostability and Protection Against Emerging VOCs)

The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 or a third and potentially a fourth dose of prototype BNT162b2$_{SA}$.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

8.17.1. Visit 301 – Vaccination 3: (150 to 210 Days After Visit 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of a third dose of BNT162b2, he or should remain on the Phase 2/3 visit schedule.

Note: This visit can occur on the same day as Visit 4, but all procedures for both visits must be conducted (including collection of all blood samples).

- Confirm that the participant originally received BNT162b2 at Vaccinations 1 and 2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Record nonstudy vaccinations as described in Section 6.5.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 1, 2, 3, 5, and 6 are met and exclusion criteria 1, 3, 5, 8, 10, 11, 12, 13, 15, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Obtain the participant's randomization number and study intervention allocation number using the IRT system. **The IRT system will also assign an additional single participant number; this number will not be used as the primary identifier for the participant, but must be included in the participant's source documents and transcribed into the CRF**. The system will also identify those participants who are to receive a fourth dose; this should be kept blinded until from the participant until Visit 303.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

  - Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

  - Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):

    - Fever ≥39.0°C (≥102.1°F)

    - Redness or swelling at the injection site measuring greater than 10 cm (≥20 measuring device units)

    - Severe pain at the injection site

    - Any severe systemic event

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.17.2. Visit 302 – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 301)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.17.3. Visit 303 – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 301)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.

Only if the participant is to receive a further dose of BNT162b2$_{SA}$:

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 1, 2, 3, 5, and 6 are met and exclusion criteria 1, 3, 5, 8, 10, 11, 12, 13, 15, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):

  - Fever ≥39.0°C (≥102.1°F)

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)

  - Severe pain at the injection site

  - Any severe systemic event

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.17.4. Visit 304 – 1-Week Follow-up Visit (Vaccination 4): (6 to 8 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$

- Record AEs as described in Section 8.3.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Discuss contraceptive use as described in Section 10.4.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.5. Visit 305 – 1-Month Follow-up Visit (Vaccination 4): (28 to 35 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

8.17.6. Visit 306 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 301):

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.17.7. Visit 307 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 301):

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record latest CD4 count and HIV viral load.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

8.18. Administration of BNT162b2$_{SA}$ to BNT162b2-naïve Participants

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

8.18.1. Visit 401 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - Provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the study intervention accountability records.

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.18.2. Visit 402 – Vaccination 2: (19 to 23 Days After Visit 401)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the study intervention accountability records.

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.18.3. Visit 403 – 1-Week Follow-up Visit (After Vaccination 2): (6 to 8 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

8.18.4. Visit 404 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.18.5. Visit 405 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.18.6. Visit 406 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 402)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.19. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11 until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The surveillance will be conducted per the procedures listed below.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

8.19.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11

Before surveillance begins and any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

The visit should be conducted only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1) and this visit should be temporarily delayed until the symptoms have resolved.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 3 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Record AEs as described in Section 8.3 (only if the participant remains in the AE reporting period; see Section 8.3.1).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Ask the participant to obtain a surveillance self-swab at home in approximately 14 days or schedule an appointment for the participant to return to collect the swab at the site. The swab should be collected only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1).

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.19.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection

This is a repeating swab collection and will be conducted approximately every 14 days until the intensive surveillance period ends.

- Participant collects a self-swab and ships it to the site for assessment at the central laboratory. The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- Complete the source documents with the swab information.

- The investigator or an authorized designee completes the CRFs with the swab information.

8.20. Administration of a Third Dose of BNT162b2 to Participants Who Have Not Previously Received a Third Dose

The opportunity to receive a third dose of BNT162b2 will be offered as part of the study, according to recommendations detailed separately, and available in the electronic study reference portal.

The additional information collected at Visits 501, 502, 503, and 504 will be collected in a supplementary database; further information on the recording of this information will be provided in the study CRF Completion Requirements document.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.20.1. Visit 501 – Third Dose of BNT162b2

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant has only received 2 doses of BNT162 as part of the study and not outside. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant (and meets local recommendations/guidelines), vaccination may proceed, even if inclusion criteria are not met (excluding inclusion criterion 6, which must be met in all cases) and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.21.)

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.20.2. Visit 502 – 1-Month Follow-up Telephone Contact: (28 to 35 Days After Visit 501)

- Contact the participant/participant's parent(s)/legal guardian by telephone.

- Record AEs as described in Section 8.3.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 501 (if any).

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.20.3. Visit 503 – 6-Month Follow-up Telephone Contact: (175 to 189 Days After Visit 501)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 502 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.20.4. Visit 504 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 501):

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 503 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.21. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after the third dose of BNT162b2 should be specifically evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis.

In addition to a clinical evaluation, the following should be performed:

- ECG and
- Measurement of the troponin level

If myocarditis or pericarditis is suspected based upon the initial evaluation, the following should also be performed:

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study

Details of the symptoms reported and results of the investigations performed, will be recorded in the CRF.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by all-available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either VE_1 >30% or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated based on the lower bound of the 95% CI. VE will be demonstrated if the lower bound of the 2-sided 95% CI for VE is >20%.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

9.1.2.2.1. Hypothesis for Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2**.** If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

9.1.2.2.2. Hypotheses for Boostability and Protection Against Emerging SARS-CoV-2 VOCs

The primary and secondary objectives for boostability and protection against emerging VOCs for BNT162b2-experienced participants and BNT162b2-naïve participants will be assessed based on:

- GMRs of SARS-CoV-2 SA and/or reference strain neutralizing titers using a 1.5-fold noninferiority margin. Noninferiority is met if the lower limit of the alpha adjusted CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.8.

- The difference in percentages of participants with seroresponse to SA and/or reference strain using a 10% noninferiority margin. Noninferiority is met if the lower limit of the alpha-adjusted CI for the difference in percentages of participants with seroresponse is >-10%.

Seroresponse is defined as achieving ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

9.1.2.2.2.1. Multiplicity Control for the Boostability and Protection-Against-VOCs Objectives

Figure 1 outlines the type I error control strategy for multiple objectives across different populations (BNT162b2-experienced or BNT162b2-naïve) and estimands (GMR or seroresponse).

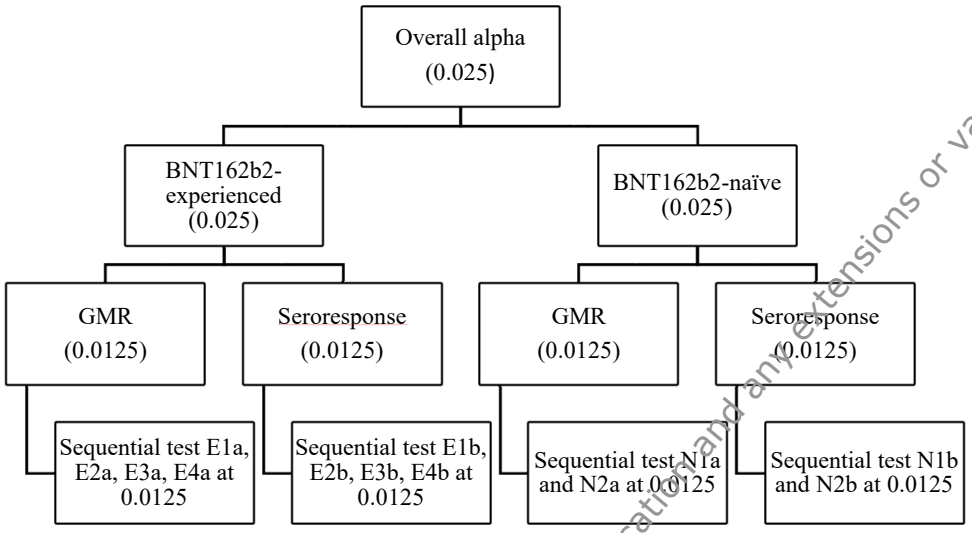
The objectives for BNT162b2-experienced participants and BNT162b2-naïve participants will be evaluated independently. The vaccine-experienced and -naïve individuals are different populations with different objectives. The 2 populations are included in the same study to improve operational efficiency. Therefore, no type I error adjustments will be applied to the assessments of the 2 populations.

For each population, the objectives will be evaluated separately for each estimand. To control the overall type I error, the 1-sided alpha of 0.025 will be split and allocated equally to each estimand. Specifically, for each estimand, the hypotheses will be tested in sequential order (as listed in the objectives in Section 3) using a 1-sided alpha of 0.0125 (Figure 1, where E and N represent vaccine-experienced and vaccine-naïve, respectively, and a and b represent GMR and seroresponse estimands, respectively).

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Figure 1. Multiplicity Schema



9.2. Sample Size Determination

9.2.1. Phase 1

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

9.2.2. Efficacy Against COVID-19

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

9.2.3. Efficacy Against Asymptomatic Infection

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection will be assessed in Phase 2/3 participants (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT). Assuming a true VE of 70%, a total of 53 asymptomatic cases will provide approximately 90% power to conclude true VE >20%. A total of 206 cases is needed to have 90% power if the true VE is 50%. The hypothesis for asymptomatic seroconversion of N-binding antibody will be tested if at least 206 cases are accrued. The hypothesis for asymptomatic infection based on central laboratory–confirmed NAAT in participants who are consented to participate in the intensive surveillance phase will be tested if at least 53 cases are accrued.

9.2.4. Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 280 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.65	-0.2	225	90.4%

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer.
a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).
b. At 0.05 alpha level (2-sided).

9.2.5. Boostability and Protection Against Emerging SARS-CoV-2 VOCs

To assess boostability and protection against emerging SARS-CoV-2 VOCs, approximately 300 participants will be enrolled in each of the 3 groups (BNT162b2-experienced participants to receive either a third dose of BNT162b2 at 30 µg [Group 1] or a third dose of BNT162b2$_{SA}$ [Group 2], BNT162b2-naïve participants to receive 2 doses of BNT162b2$_{SA}$ [Group 3]) to provide an acceptable safety database.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Assuming 20% nonevaluable rate, approximately 240 evaluable participants in each group will contribute to immunogenicity evaluation. This will provide sufficient power for noninferiority evaluations with appropriate multiplicity adjustment for type I error control.

For comparisons based on GMR, the assay standard deviation in log scale is assumed to be 0.74 based on results from Phase 2 of the study and adjusted for assay variability. A GMR of 1 is assumed for each comparison.

For comparisons based on seroresponse, a 90% response rate is assumed for each comparative group or at each comparative time point.

Within-Group Comparison for BNT162b2-Experienced Participants

For each randomized group of BNT162b2-experienced participants (Group 1: received a third dose of BNT162b2 at 30 μg and Group 2: received a third dose of $BNT162b2_{SA}$), with 240 evaluable participants and the stated assumptions for the GMR and standard deviation, the study has >99.9% power to demonstrate NI based on GMR for the objectives in vaccine-experienced individuals using a 1.5-fold margin.

Assuming true response rate of 90% at each time point and 10% of the participants having a different response status at 2 comparative timepoints, the study has 99% power to show NI based on seroresponse rate for the objectives in vaccine-experienced individuals using a 10% margin. The study will have 89% power to show NI if 20% of the participants have a different response status at 2 comparative timepoints.

Between-Group Comparison of BNT162b2-Naïve Participants to Selected Existing Phase 3 Participants Who Received 2 Doses of BNT162b2

Approximately 300 participants will be selected from the existing Phase 3 participants who received 2 doses of BNT162b2 to form the control group for the BNT162b2-naïve participants. The selection will ensure comparable distribution of age, sex, and other demographic factors in the control group and BNT162b2-naïve group. With 240 evaluable BNT162b2-naïve participants and 240 evaluable participants in the control group and the above stated assumptions for the GMR, standard deviation, and seroresponse rate, the study has >99.9%% power to declare NI based on GMR for the objectives in vaccine-naïve individuals using a 1.5-fold margin and 89.7% power to declare NI based on seroresponse rate using a 10% margin.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

9.2.6. Safety

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=300	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.03	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.06	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.11	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.16	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.21	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.26	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.36	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.45	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.53	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.59	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.65	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.78	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	0.95	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 3 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 (or BNT162b1 for Phase 1) as initially randomized, with Dose 2 received within the predefined window, receive a third dose of BNT162b2 or BNT162b2$_{SA}$ as rerandomized (or receive a third dose of BNT162b2 for Phase 1), have at least 1 valid and determinate immunogenicity result after Dose 3 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 4 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 as initially randomized, with Dose 2 received within the predefined window, receive 2 booster doses of BNT162b2$_{SA}$ as rerandomized, have at least 1 valid and determinate immunogenicity result after Dose 4 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emea-eropaeu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Population	Description
Dose 3 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 (or BNT162b1 for Phase 1) at initial randomization, receive a third dose of BNT162b2 or BNT162b2$_{SA}$ at rerandomization (or receive a third dose of BNT162b2 for Phase 1), and have at least 1 valid and determinate immunogenicity result after Dose 3.
Dose 4 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 at initial randomization, receive 2 booster doses of BNT162b2$_{SA}$ at rerandomization, and have at least 1 valid and determinate immunogenicity result after Dose 4.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
Evaluable efficacy (seroconversion)	All eligible randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window, have at least 1 N-binding antibody test result available at a post–Dose 2 visit, and have no other important protocol deviations as determined by the clinician prior to the first post–Dose 2 N-binding antibody test.
Evaluable efficacy (asymptomatic surveillance)	All eligible randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window, consent to participate in the asymptomatic surveillance, and have no other important protocol deviations as determined by the clinician on or before the start of the asymptomatic surveillance period.
All-available efficacy	Dose 1 all-available: All randomized participants who receive at least 1 vaccination. Dose 2 all-available: All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention. Analyses of reactogenicity endpoints will be based on a subset of the safety population that includes participants with any e-diary data reported after vaccination.
Booster safety	All participants who receive at least 1 booster dose of the study intervention.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Empirical RCDCs will be provided for all immunogenicity analyses.

Endpoint	Statistical Analysis Methods
Primary immunogenicity (Phase 3, boostability and protection against emerging VOCs)	In order to allow direct comparability with the reference strain, the anti-SA NTs may be adjusted to account for intrinsic variant or assay characteristics. The small group of existing Phase 3 participants who are to receive a third and fourth dose of BNT162b2$_{SA}$ will not be included in the primary and secondary analyses except for the last secondary descriptive objective. ***<u>BNT162b2-Experienced Participants:</u>*** **E1a: GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 in the same individuals** **E2a: GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** The comparisons of different NTs (anti-SA or anti–reference strain) or the same NTs at different time points within the same group will be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Endpoint	Statistical Analysis Methods
	limited to participants with nonmissing values at both time points or both NT measurements. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (eg, later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 97.5% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. Noninferiority of E1a and E2a will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8. **E1b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2 in the same individuals** **E2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** Similar to E1a and E2a, the within-group comparisons of seroresponse to different NTs (anti-SA or anti–reference strain) or the same NTs at different time points within the same group will be limited to participants with nonmissing values at both time points or both NT measurements. The percentages of participants with seroresponse at each time point and the difference in percentages will be provided. The 2-sided 97.5% CIs for the difference in percentages of participants with seroresponse will be calculated using the adjusted Wald interval as described by Agresti and Min (2005)[11] for comparing matched proportions. Noninferiority of E1b and E2b will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%. ***BNT162b2-Naïve Participants:*** **N1a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2**

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	For the between-group comparison, GMRs will be calculated as the mean of the difference of logarithmically transformed assay results between 2 groups and exponentiating the mean. The associated 2-sided 97.5% CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed titers and exponentiating the confidence limits. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8. **N1b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2** The difference in percentages of participants with seroresponse and associated 2-sided 97.5% CIs will be calculated using the Miettinen and Nurminen method.[12] Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%.
Secondary immunogenicity (Phase 3, boostability and protection against emerging VOCs)	***BNT162b2-Experienced Participants:*** **E3a: GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** **E4a: GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 in the same individuals** **E3b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** **E4b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2 in the same individuals**

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	GMRs and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1a and E2a. If noninferiority of E1a and E2a are both established, E3a and E4a will be assessed sequentially using the same criterion (lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8). The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. Similarly, if noninferiority of E1b and E2b are both established, E3b and E4b will be assessed sequentially using the same criterion (lower bound of the 2-sided 97.5% CI for the difference in percentages is greater than -10%). **GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg** **The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints N1b. **GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** **The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint E1a and E2a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Endpoint	Statistical Analysis Methods
	the primary endpoints E1b and E2b. ***BNT162b2-Naïve Participants:*** **N2a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2** **N2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2** GMR and the associated 2-sided 97.5% CI will be calculated in the same way as for the primary endpoint N1a. Statistical superiority of N2a will be assessed if noninferiority of N1a is established. Superiority of N2a will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 1. The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints N1b. Statistical superiority of N2b will be assessed if noninferiority of N1b is established. Superiority of N2b will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than 0%. **GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2** **The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints N1b.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Endpoint	Statistical Analysis Methods
Secondary immunogenicity (Phase 1)	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Endpoint	Statistical Analysis Methods
16- to 25-year age group)	2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment. The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2: **GMTs/GMCs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level** GMTs/GMCs and 2-sided 95% CIs will be provided by initial vaccine and age group for the following time points: • At Dose 3 and 7 days and 1 month after Dose 3 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level** GMFRs from before Dose 3 to 7 days and 1 month after Dose 3 and 2-sided 95% CIs will be provided by initial vaccine and age group. GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **GMRs of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2** GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed reference-strain titers for each participant (1 month after Dose 3 – 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. **GMRs of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2** GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (SA-variant titer at 1 month after Dose 3 – reference-strain titer at 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.
Exploratory immunogenicity (Phase 2/3)	**GMTs/GMCs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3:

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Endpoint	Statistical Analysis Methods
	• 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Endpoint	Statistical Analysis Methods
	RCDCs for immunogenicity results Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels after Dose 1 and after Dose 2.
Exploratory immunogenicity (Phase 3, boostability and protection against emerging VOCs)	**GMTs of SARS CoV-2 reference strain neutralizing titers in participants receiving a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$** GMTs and associated 2-sided 95% CIs at Dose 3 and each subsequent time point will be provided for each vaccine group and age group. **GMFRs of SARS CoV-2 reference strain neutralizing titers in participants receiving a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$** GMFRs from Dose 3 to each subsequent time point and associated 2-sided 95% CIs will be provided for each vaccine group and age group. **Geometric mean NT for any VOC not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2** Geometric means and associated 2-sided 95% CIs of any anti-VOC neutralizing titers will be provided at each time point for each group.

9.4.2. Efficacy Analyses

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Endpoint	Statistical Analysis Methods
	in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.
Secondary	**First: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Second: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Endpoint	Statistical Analysis Methods
	Third and fourth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group **Fifth and sixth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints for COVID-19 illness according to CDC-defined symptoms will be evaluated descriptively with 95% CIs. **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days or from 14 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[10] Missing efficacy data will not be imputed.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	The following secondary efficacy endpoints regarding asymptomatic SARS-CoV-2 infection will be evaluated based on a success criterion of the lower bound of the 2-sided 95% CI for VE being >20%. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate per 1000 person-years of follow-up in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The hypothesis will be tested if at least 206 cases are accrued. In addition, a descriptive summary of VE against asymptomatic infection over different time intervals (ie, prior to 1 month after Dose 2, from 1 month after Dose 2 onward), along with the associated 2-sided 95% CI, will be calculated using the same method. The analysis of the primary definition of asymptomatic cases will be based on the evaluable efficacy (seroconversion) population and the Dose 2 all-available efficacy population. The analysis of the secondary definition of asymptomatic cases will be based on the Dose 1 all-available efficacy population. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants without evidence of infection (up to the start of asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The hypothesis will be tested if at least 53 cases are accrued. The analysis will be based on the evaluable efficacy (asymptomatic surveillance) population and the all-available efficacy population and will include only participants who are consented to participate in the asymptomatic surveillance and who do not have serological or

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	virological evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period.
Exploratory	**Ratios of confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants without, and with and without, evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** After the primary objectives are met at the final analysis of at least 164 first primary cases, the study will continue with blinded follow-up until the participant is unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. A descriptive update of VE will be provided with additional follow-up data. VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[10] Supportive analysis of time to confirmed COVID-19 illness will be performed using Kaplan-Meier cumulative incidence curves. Participants who were randomized to placebo will be censored at the time of receipt of BNT162b2. **Incidence of confirmed COVID-19 through the entire study follow-up period prior to receiving the third dose of BNT162b2 in participants who received BNT162b2** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness from 7 days after the second dose will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Endpoint	Statistical Analysis Methods
	Incidence of confirmed COVID-19 after receiving the third dose of BNT162b2 Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness from 7 days after the third dose of BNT162b2 will be provided. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted. **Incidence of asymptomatic SARS-CoV-2 infection through the entire study follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants who received BNT162b2 and who have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for asymptomatic infection will be provided for participants who received BNT162b2 at initial randomization and have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with evidence of infection (up to the start of the asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. Participants who are consented to participate in the asymptomatic surveillance and who have serological or virologic evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period will be included in the analysis.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[12] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Endpoint	Statistical Analysis Methods
	SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group. AEs and SAEs reported during the open-label follow-up period will be summarized separately for participants who were unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. For Phase 3 participants enrolled for assessment of boostability and protection against emerging VOCs, descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for local reactions and systemic events from Day 1 through Day 7 after each dose, AEs from Dose 1 to 1 month after the last dose, and SAEs from Dose 1 to 5 or 6 months after the last dose. Local reactions and systemic events from Day 1 through Day 7 after each dose will be presented by severity and cumulatively across severity levels. For participants who received the third dose of BNT162b2 as part of protocol amendment 18, descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for AEs from Dose 3 to 1 month after Dose 3, and SAEs from Dose 3 to 6 months after Dose 3. The safety analyses after the first dose and after booster dose(s) are based on the safety population and booster safety population, respectively. Analyses of reactogenicity endpoints are based on a subset of the safety population that includes participants with any e-diary data reported after vaccination. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2: Descriptive statistics will be provided by initial vaccine and age group for local reactions and systemic events from Day 1 through Day 7 after Dose 3, and AEs/SAEs from Dose 3 to 1 month after Dose 3.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Endpoint	Statistical Analysis Methods
	Local reactions and systemic events from Day 1 through Day 7 after Dose 3 will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs.

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GMFR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" and each lot of "Process 2" will be summarized descriptively. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected randomly for the analysis.

Exploratory analyses to investigate possible immunological correlates with efficacy, and characterization of infecting SARS-CoV-2 variants, may be conducted.

The cell-mediated immune response and additional humoral immune response parameters to the reference strain and SA will be summarized for the subset of participants with PBMC samples collected.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 6 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8, for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

Only the first primary endpoint will be analyzed at IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints (confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and in all

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

participants, confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection and in all participants) will be evaluated sequentially in the stated order, by the same method used for the evaluation of primary VE endpoints. Success thresholds for secondary VE endpoints will be appropriately chosen to control overall type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Complete safety and immunogenicity analysis approximately 1 month after Dose 3 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data (with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.
- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.
- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.
- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2.
- Safety analyses approximately 1 month after Dose 3 for Phase 3 participants included in the booster evaluation (30 µg or low-dose booster) and approximately 1 month after Dose 2 for newly enrolled Phase 3 participants included in the BNT162b2$_{SA}$ evaluation.
- Immunogenicity analyses approximately 1 month after Dose 3 for Phase 3 participants included in the booster evaluation (30 µg or low-dose booster) and approximately 1 month after Dose 2 for newly enrolled Phase 3 participants included in the BNT162b2$_{SA}$ evaluation, when serology data for the reference strain or for the SA strain are available.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Analysis of efficacy against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) when a sufficient number of cases have accrued to evaluate the objective(s).

- Complete safety and efficacy analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.

- Safety and efficacy analyses approximately 6 months after the third dose of BNT162b2 for participants who received a third dose of BNT162b2 as part of protocol amendment 18.

- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort

- Review of safety data in the case of a stopping rule being met

- Review of safety and/or immunogenicity data to:

  - Allow groups of participants of 65 to 85 years of age to proceed

  - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review

- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:

  - Whether any groups may not be started

  - Whether any groups may be terminated early

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses

- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule

- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule

- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Up until the final efficacy analysis, 3 blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial. When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. • Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE/SAE CRF page.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
20vPnC	20-valent pneumococcal conjugate vaccine
Abs	absolute (in Appendix 2)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCR	B-cell receptor
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
E1, E2, etc	vaccine-experienced (statistical tests)
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N1, N2, etc	vaccine-naïve (statistical tests)
N/A	not applicable
NAAT	nucleic acid amplification test
NI	noninferiority
non-S	nonspike protein
NT	neutralizing titer
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SA	South Africa
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
TCR	T-cell receptor
UK	United Kingdom
ULN	upper limit of normal
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
VOC	variant of concern
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs after accrual of at least 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.9. Appendix 9: Genetics

Use/Analysis of DNA and/or RNA

- Genetic variation may impact a participant's response to study intervention, as well as susceptibility to and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA and/or RNA analysis.
- The results of genetic analyses may be reported in a CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA and/or RNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
  - Samples for specified genetic analysis (see Section 8.7) will be stored for up to 15 years or other period as per local requirements.
- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 World Health Organization. COVID-19 Weekly Epidemiological Update - 55. Data as reported by national authorities as of 29 August 2021. Geneva, Switzerland: World Health Organization; 2021.

4 Centers for Disease Control and Prevention. Emerging SARS-CoV-2 variants. Available from: https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html. Updated: 28 Jan 2021. Accessed: 10 Feb 2021.

5 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

6 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

7 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

8 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

9 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

10 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

11 Agresti A, Min Y. Simple improved confidence intervals for comparing matched proportions. Stat Med 2005;24(5):729-40.

12 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 18 Clean Copy, 07Sep2021
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	07-Sep-2021 16:13:38	Business Line Approver
PPD	07-Sep-2021 17:53:07	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e198027d65\Approved\Approved On: 07-Sep-2021 17:53 (GMT)

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 17	20 July 2021	• Changed the analysis method for the within-group comparison of seroresponse rates for Phase 3 booster and VOC immunogenicity assessment from the Miettinen and Nurminen method to the adjusted Wald interval to provide tighter CI and higher power for NI in most cases. • Clarified that any nonstudy coronavirus vaccines are to be recorded at any time they are given during study participation. • Clarified that participants who are randomized in the C4591031 study should be withdrawn from this study.
Protocol amendment 16	28 May 2021	• Removed the requirement to conduct a potential COVID-19 convalescent visit following each potential COVID-19 illness visit. • Clarified that only non-Pfizer interventional studies for prevention of COVID-19 are prohibited throughout study participation. • Clarified that during the 7 days following each vaccination (either as part of this study, co-enrolled C459 studies, or the B7471026 [20vPnC] study), potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. • Revised the noninferiority margin from 2-fold to 1.5-fold and added a minimum GMR point estimate of ≥0.8 as another success criterion for Phase 3 booster and VOC immunogenicity assessment. Noninferiority is met if the lower limit of the alpha-adjusted CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.8. • Added Phase 1 booster participants to the Dose 3 booster immunogenicity population definitions. • Included a booster safety population definition. • Clarified that the interim analyses for booster immunogenicity will be conducted when serology data for the reference strain or for the SA strain are available.
Protocol amendment 15	25 March 2021	• In order to further characterize booster responses induced by BNT162b2, 2 additional lower-dose booster groups have been added to the subset for evaluation of boostability and protection against

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		emerging VOCs. An additional 5-µg or 10-µg dose of BNT162b2 will be given to approximately 144 Phase 3 participants approximately 5 to 7 months after their second dose of BNT162b2. • To further describe cell-mediated immune responses following isolations of PBMCs in a subset of both the Phase 3 participants who receive a single booster vaccination and the BNT162b2-naïve group who receive BNT162b2$_{SA}$, additional genetic testing may also be performed; corresponding details and an appendix have been added. • An exploratory objective was added for Phase 3 participants to describe the immune response to a third dose of BNT162b2 or a third or fourth dose of BNT162b2$_{SA}$ at later time points to align with analyses and corresponding changes detailed in the statistical section. • Removed the lower age limit for eligibility for administration of BNT162b2 to those originally assigned to placebo: this will now be covered in the recommendations detailed separately, and available in the electronic study reference portal. • Allowed administration of BNT162b2 at Visits 101 and 102 to pregnant participants in certain circumstances. • To align with contraception requirements, reduced the EDP reporting period to 28 days after the last dose of study intervention.

Protocol amendment 14	02 March 2021	• In order to further describe duration of protection, and heterologous/homologous protection against the emerging VOCs, an additional dose of BNT162b2 or BNT162b2$_{SA}$ will be given to approximately 600 Phase 3 participants approximately 5 to 7 months after their second dose of BNT162b2; a further dose of BNT162b2$_{SA}$ will be given to approximately 30 of those participants who receive BNT162b2$_{SA}$:
		  • Added corresponding objectives, estimands, and endpoints
		  • Added corresponding SoA and procedures
		  • Added details in the statistical methods sections.
		• Approximately 300 BNT162b2-naïve participants will be enrolled and receive 2 doses of BNT162b2$_{SA}$ to describe

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		heterologous/homologous protection against the emerging VOCs and reference strains: • Added corresponding objectives, estimands, and endpoints • Added corresponding SoA and procedures • Added details in the statistical methods sections. • Cell-mediated immune responses will also be described following isolations of PBMCs in a subset of both the Phase 3 participants who receive a single booster vaccination and the BNT162b2-naive group who receive BNT162b2$_{SA}$. • Added the asymptomatic case definitions in Section 8.1 and further clarified the secondary definition for asymptomatic case based on seroconversion of N-binding antibody. • Defined the analysis populations used for evaluation of asymptomatic infection based on seroconversion of N-binding antibody and based on NAAT from participants who consent to active surveillance. • Clarified that unblinding for a nonemergency reason should be conducted outside of the IRT system. • Clarified that if multiple visits occur on the same day, all procedures for all visits must be conducted (including collection of all blood samples). • Clarified the plan for stepwise unblinding of the sponsor in the study.
Protocol amendment 13	12 February 2021	• In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2: • Added corresponding objectives, estimands, and endpoints • Added corresponding SoA and procedures • Added details in the statistical methods sections. • Clarified the population used for analysis of reactogenicity endpoints. • To align with current recommendations, investigators may exercise judgment on review of inclusion and exclusion criteria ahead of

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		vaccination with BNT162b2 for participants who originally received placebo. • Clarified that if a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent. • Participants who provide biweekly swabs for surveillance of asymptomatic infection should now continue to swab even after unblinding if they originally received BNT162b2, to maximize the numbers of swabs to be collected. • Clarified the procedures for unscheduled visits to administer a second dose in the event a participant received only 1 dose of BNT162b2.
Protocol amendment 12	14 January 2021	• Because of a formatting error in protocol amendment 11, exclusion criterion 4 was inadvertently added to exclusion criterion 3 and the subsequent criteria renumbered. This amendment corrects that error. • Because of a change in the pace with which participants ≥16 years of age who originally received placebo will become eligible for receipt of BNT162b2, text was updated throughout the protocol to reflect that this will happen in a phased manner, with recommendations detailed separately and available in the electronic study reference portal. • Clarified that participants who are unblinded because they become potentially eligible for receipt of BNT162b2 will not participate in surveillance for asymptomatic SARS CoV-2 infection. • Corrected the exploratory objective to describe non-S seroconversion to SARS-CoV-2 to clarify that this will only include participants who received BNT162b2 at initial randomization (since those who received it subsequently do not have blood drawn). • In line with current recommendations, removed the requirement to discontinue study intervention because of a diagnosis of COVID-19 during the study.
Protocol amendment 11	04 January 2021	• Added approaches to evaluate efficacy against asymptomatic SARS-CoV-2 infection: • Added objectives, estimands, and endpoints, and statistical methods, for assessment via N-binding antibody seroconversion;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**

		• Added a potential intensive surveillance period for nasal swabbing, for assessment via NAAT:
		  • Corresponding objectives, estimands, and endpoints added
		  • Corresponding SoA and procedures added
		  • Details added in the statistical methods sections.
		• Added the possibility of assessing full-length S-binding, instead of S1-binding, IgG levels in Phase 2/3.
		• Clarified in Section 4.1.1 that any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity at the approximate time participants in Phase 2/3 reach Visit 4, for consistency with other sections.
		• Added a sentence to reflect that assent is obtained from participants <18 years of age.

Protocol amendment 10	01 December 2020	• Added the possibility of administering BNT162b2 to participants who originally received placebo, following any local or national recommendations. • Added the possibility of administering BNT162b2 to participants who originally received placebo, following completion of the active safety surveillance period. • Added corresponding exploratory objectives and statistical analysis details. • Removed immunogenicity analyses of titers greater than defined threshold(s). • Removed the need for blinded COVID-19 case review after the final efficacy analysis. • Included the possibility, due to local circumstances related to the COVID-19 pandemic, that study procedures that do not require in-person participant contact may be performed by telehealth. • In light of additional information to better estimate the standard deviation of SARS-CoV-2 neutralizing titers, increased the sample size for the noninferiority immunogenicity analysis in adolescents 12 to 15 years of age.
Protocol amendment 9	29 October 2020	• To better align with the natural history of SARS-CoV-2 infection, added Phase 2/3 secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days after the second dose; also

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		modified the existing secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days, as well as 7 days, after the second dose; • Made corresponding changes to the study design, study assessments and procedures, and statistical analysis sections. • For operational reasons, removed the interim analysis planned after accrual of 32 cases. • Clarified that interim analyses will be conducted after accrual of *at least* 62, 92, and 120 cases. • Included any participants 16 through 17 years of age enrolled under this amendment in the reactogenicity subset. • Added an unblinded clinical scientist to support DMC activities. • Clarified that serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.
Protocol amendment 8	15 October 2020	• Removed "N-binding antibody" and "SARS-CoV-2 detection by NAAT" as endpoints from the third exploratory objective, as these results are used for the determination of the population, and are not endpoints. • Clarified that the "Process 1" participants included in the descriptive analysis of "Process 1"- and "Process 2"-manufactured study interventions will be selected randomly. • Clarified that surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study. • Further modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Clarified that for participants who are not in the reactogenicity subset, local reactions and systemic events following vaccination should be detected and reported as AEs. • Clarified that premenarchal females are not WOCBP. • Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2." • Clarified the degree of unblinding on the unblinded submissions team in Section 6.3.3. • Made provision for a second dose of BNT162b2 in participants who were affected by a medication error at Visit 2 in Section 6.6. • Provided further clarification regarding discontinuation of study intervention in Section 7.1. • Modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Added that 2 periods of potential COVID-19 symptoms within 4 days will be considered as a single illness. • Provided guidance in Section 8.13 regarding circumstances in which a SARS-CoV-2 test might be required even if symptoms within 7 days following each vaccination are considered more likely due to vaccine reactogenicity. • Made allowance in Section 8.13 for a second SARS-CoV-2 test to be performed within the same potential COVID-19 illness if it is in accordance with routine practice. • Added Section 8.15 to describe the reporting of SARS-CoV-2 test results and their implications for participants receiving a second vaccine dose. • Added statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age. • Amended scope of analyses of safety data in Section 9.5.1. • Made various editorial changes.
Protocol amendment 6 (Germany-specific)	23 September 2020	• According to regulatory request, inclusion criterion 1 now specifies that participants less than 18 years of age will not be enrolled in the EU.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 6	08 September 2020	• Reordered some procedures in the Phase 2/3 schedule of activities for consistency with the main body of the protocol. • Corrected the window for the 6-month follow-up visit to be approximately 6 months after Vaccination 2. • Reduced the volume of blood draws to ~20 mL. • Removed the need to have safety data reported for participants to be included in the safety objective assessment. • Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease. • Increased the sample size for Phase 2/3 to ~43,998. • Clarified that inclusion criterion 4 (ie, participants at higher risk for acquiring COVID-19) is applicable for Phase 2/3 only, and provided some examples. • Removed exclusion criterion 2 (ie, known infection with HIV, HCV, or HBV) for Phase 3 and added criteria for HIV-positive participants. • Decreased the lower age limit and removed the upper age limit for inclusion in Phase 2/3 in order to evaluate BNT162b2 30 µg in older adolescents and those over 85 years of age; updated the title and other references to adults to align with this change. • Renamed the immunological assays to align with other program-level documents. • Removed reference to the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) being “heads up.” • Clarified that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention. • Added clarification that potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. • Updated the analysis population descriptions to align with the study SAP.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory. • Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7. • Updated the stopping and alert rule parameters for enhanced COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 23
LIST OF FIGURES 23
1. PROTOCOL SUMMARY 24
1.1. Synopsis 24
1.2. Schema 38
1.3. Schedule of Activities 39
1.3.1. Phase 1 39
1.3.2. Phase 2/3 46
1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo 50
1.3.4. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) 52
1.3.5. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants 55
1.3.6. Surveillance for Asymptomatic SARS-CoV-2 Infection 58
2. INTRODUCTION 59
2.1. Study Rationale 59
2.2. Background 59
2.2.1. Clinical Overview 61
2.3. Benefit/Risk Assessment 61
2.3.1. Risk Assessment 63
2.3.2. Benefit Assessment 65
2.3.3. Overall Benefit/Risk Conclusion 65
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 65
3.1. For Phase 1 65
3.2. For Phase 2/3 67
4. STUDY DESIGN 74
4.1. Overall Design 74
4.1.1. Phase 1 75
4.1.2. Phase 2/3 76
4.2. Scientific Rationale for Study Design 79
4.3. Justification for Dose 79

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

4.4. End of Study Definition 80
5. STUDY POPULATION 81
5.1. Inclusion Criteria 81
5.2. Exclusion Criteria 82
5.3. Lifestyle Considerations 85
5.3.1. Contraception 85
5.4. Screen Failures 85
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 85
6. STUDY INTERVENTION 86
6.1. Study Intervention(s) Administered 87
6.1.1. Manufacturing Process 87
6.1.2. Administration 88
6.2. Preparation/Handling/Storage/Accountability 88
6.2.1. Preparation and Dispensing 89
6.3. Measures to Minimize Bias: Randomization and Blinding 90
6.3.1. Allocation to Study Intervention 90
6.3.2. Blinding of Site Personnel 90
6.3.3. Blinding of the Sponsor 91
6.3.4. Breaking the Blind 92
6.4. Study Intervention Compliance 92
6.5. Concomitant Therapy 93
6.5.1. Prohibited During the Study 93
6.5.2. Permitted During the Study 94
6.6. Dose Modification 94
6.7. Intervention After the End of the Study 95
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 95
7.1. Discontinuation of Study Intervention 95
7.2. Participant Discontinuation/Withdrawal From the Study 96
7.2.1. Withdrawal of Consent 97
7.3. Lost to Follow-up 97

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8. STUDY ASSESSMENTS AND PROCEDURES 98
8.1. Efficacy and/or Immunogenicity Assessments 99
8.1.1. Efficacy Against COVID-19 99
8.1.2. Efficacy Against Asymptomatic SARS-CoV-2 Infection 101
8.1.2.1. Seroconversion of N-Binding Antibody 101
8.1.2.2. NAAT-Confirmed SARS-CoV-2 Infection 101
8.1.3. Vaccine-Induced Immunogenicity 102
8.1.4. Biological Samples 102
8.1.5. Surveillance for Asymptomatic SARS-CoV-2 Infection 103
8.2. Safety Assessments 103
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 104
8.2.2. Electronic Diary 104
8.2.2.1. Grading Scales 105
8.2.2.2. Local Reactions 105
8.2.2.3. Systemic Events 106
8.2.2.4. Fever 107
8.2.2.5. Antipyretic Medication 108
8.2.3. Phase 1 Stopping Rules 108
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 109
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 110
8.2.6. Pregnancy Testing 110
8.3. Adverse Events and Serious Adverse Events 110
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 111
8.3.1.1. Reporting SAEs to Pfizer Safety 112
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 112
8.3.2. Method of Detecting AEs and SAEs 112
8.3.3. Follow-up of AEs and SAEs 113
8.3.4. Regulatory Reporting Requirements for SAEs 113
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 113
8.3.5.1. Exposure During Pregnancy 113

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

8.3.6. Exposure During Breastfeeding 115
8.3.6.1. Occupational Exposure 115
8.3.7. Cardiovascular and Death Events 116
8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 116
8.3.9. Adverse Events of Special Interest 116
8.3.9.1. Lack of Efficacy 116
8.3.10. Medical Device Deficiencies 117
8.3.11. Medication Errors 117
8.4. Treatment of Overdose 118
8.5. Pharmacokinetics 118
8.6. Pharmacodynamics 118
8.7. Genetics 118
8.8. Biomarkers 118
8.9. Immunogenicity Assessments 119
8.10. Health Economics 119
8.11. Study Procedures 119
8.11.1. Phase 1 119
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 119
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 120
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 123
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 124
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 125
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 127
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 128
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 129
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4) 130
8.11.1.10. Between Visits 8 and 9 131

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2) 131
8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a)....133
8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a)....133
8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2....134
8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2....134
8.11.2. Phase 2/3....135
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 135
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 138
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)....140
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)....141
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 141
8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 142
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 143
8.13. COVID-19 Surveillance (All Participants) 144
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 145
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)....146
8.14. Communication and Use of Technology....146
8.15. SARS-CoV-2 NAAT Results....147

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo 148
8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2) 148
8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101) 149
8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102) 150
8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102) 151
8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102) 152
8.17. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) 152
8.17.1. Visit 301 – Vaccination 3: (150 to 210 Days After Visit 2) 152
8.17.2. Visit 302 – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 301) 154
8.17.3. Visit 303 – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 301) 155
8.17.4. Visit 304 – 1-Week Follow-up Visit (Vaccination 4): (6 to 8 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$ 157
8.17.5. Visit 305 – 1-Month Follow-up Visit (Vaccination 4): (28 to 35 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$ 157
8.17.6. Visit 306 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 301): 158
8.17.7. Visit 307 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 301): 159
8.18. Administration of BNT162b2$_{SA}$ to BNT162b2-naïve Participants 159
8.18.1. Visit 401 – Vaccination 1: (Day 1) 159
8.18.2. Visit 402 – Vaccination 2: (19 to 23 Days After Visit 401) 162
8.18.3. Visit 403 – 1-Week Follow-up Visit (After Vaccination 2): (6 to 8 Days After Visit 402) 163
8.18.4. Visit 404 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 402) 164
8.18.5. Visit 405 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 402) 165

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.18.6. Visit 406 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 402) 166
8.19. Surveillance for Asymptomatic SARS-CoV-2 Infection 166
8.19.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11 166
8.19.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection 167
9. STATISTICAL CONSIDERATIONS 168
9.1. Estimands and Statistical Hypotheses 168
9.1.1. Estimands 168
9.1.2. Statistical Hypotheses 169
9.1.2.1. Statistical Hypothesis Evaluation for Efficacy 169
9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity 169
9.2. Sample Size Determination 171
9.2.1. Phase 1 171
9.2.2. Efficacy Against COVID-19 171
9.2.3. Efficacy Against Asymptomatic Infection 172
9.2.4. Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years 172
9.2.5. Boostability and Protection Against Emerging SARS-CoV-2 VOCs 172
9.2.6. Safety 174
9.3. Analysis Sets 175
9.4. Statistical Analyses 177
9.4.1. Immunogenicity Analyses 177
9.4.2. Efficacy Analyses 187
9.4.3. Safety Analyses 192
9.4.4. Other Analyses 194
9.5. Interim Analyses 195
9.5.1. Analysis Timing 197
9.6. Data Monitoring Committee or Other Independent Oversight Committee 198
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 201
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 201

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

10.1.1. Regulatory and Ethical Considerations 201
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 201
10.1.2. Informed Consent Process 202
10.1.3. Data Protection 203
10.1.4. Dissemination of Clinical Study Data 203
10.1.5. Data Quality Assurance 204
10.1.6. Source Documents 206
10.1.7. Study and Site Start and Closure 206
10.1.8. Sponsor's Qualified Medical Personnel 207
10.2. Appendix 2: Clinical Laboratory Tests 208
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 210
10.3.1. Definition of AE 210
10.3.2. Definition of SAE 211
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 213
10.3.4. Reporting of SAEs 216
10.4. Appendix 4: Contraceptive Guidance 217
10.4.1. Male Participant Reproductive Inclusion Criteria 217
10.4.2. Female Participant Reproductive Inclusion Criteria 217
10.4.3. Woman of Childbearing Potential 218
10.4.4. Contraception Methods 219
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 221
10.6. Appendix 6: Abbreviations 223
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 227
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection 230
10.9. Appendix 9: Genetics 231
11. REFERENCES 232

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

LIST OF TABLES

Table 1. Local Reaction Grading Scale 106
Table 2. Systemic Event Grading Scale 106
Table 3. Scale for Fever 107
Table 4. Power Analysis for Noninferiority Assessment 172
Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 174
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility 196
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses 196
Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall 197
Table 9. Laboratory Abnormality Grading Scale 208
Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 228
Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 229

LIST OF FIGURES

Figure 1. Multiplicity Schema 171

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 3 antigens:

BNT162b1 (variant RBP020.3): a modRNA encoding the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5);

BNT162b2 (variant RBP020.2): a modRNA encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9);

BNT162b2s01 (variant RBP020.11): a modRNA encoding the P2 S containing South Africa B.1.351 variant-specific mutations, hereafter referred to as BNT162b2$_{SA}$, as a representative variant of concern (VOC).

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and/or efficacy of these prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	• GMCs/GMTs at the time of Dose 3 and 7 days and 1 month after Dose 3. • GMFRs from before Dose 3 to 7 days and 1 month after Dose 3 • GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2 • GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
are europa.eu

Objectives[a]	Estimands	Endpoints
To describe the safety and tolerability profile of BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants, or as 2 doses to BNT162b2-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2-experienced participants	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 5 or 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary Immunogenicity ***BNT162b2-experienced participants***		
To demonstrate the noninferiority of the anti–reference strain immune response after a third dose of BNT162b2 at 30 µg compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate the noninferiority of the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Objectives[a]	Estimands	Endpoints
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
BNT162b2-experienced participants		
To demonstrate the noninferiority of the anti-SA immune response after a third dose of BNT162b2 at 30 µg compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti–reference strain immune response after 1 dose of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ and a third dose of BNT162b2 at 30 µg	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg	SARS-CoV-2 SA NT in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$ or the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof

Objectives[a]	Estimands	Endpoints
To descriptively compare the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ and the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate a statistically greater anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 SA NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
To descriptively compare the anti–reference strain immune response after 2 doses of BNT162b2$_{SA}$ and after 2 doses of BNT162b2	GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization	In participants who received BNT162b2 at initial randomization: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate and characterize the SARS-CoV-2 isolate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers • Identification of SARS-CoV-2 variant(s)
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers
To describe the immune response to any VOCs not already specified	Geometric mean NT for any VOCs not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2	• SARS-CoV-2 NTs for any VOCs not already specified
To describe the immune response to a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$	• GMTs at Dose 3 and subsequent time points • GMFRs from Dose 3 to subsequent time points	• SARS-CoV-2 reference strain NTs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and SA in a subset of participants: • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 2 doses to BNT162b2-naïve participants • 7 Days and 1 and 6 months after BNT162b2 given as a third dose to BNT162b2-experienced participants		

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for a description of the manufacturing process.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype $BNT162b2_{VOC}$ at 30 µg (based upon the South African variant and hereafter referred to as $BNT162b2_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive $BNT162b2_{SA}$ given as a 2-dose series, separated by 21 days.

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof are europaeu

For evaluation of boostability and protection against emerging VOCs, 600 existing Phase 3 participants 18 to 55 years of age will be rerandomized in a 1:1 ratio to receive either a third dose of BNT162b2 at 30 µg or a third dose of BNT162b2$_{SA}$.

An additional group of 30 existing Phase 3 participants 18 to 55 years of age will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$. For these 30 participants, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the investigator and sponsor will not be. Serum samples from these participants may be used for assay development purposes and, except for objectives relating to response to a fourth dose, their results will be analyzed separately from the main immunogenicity analyses.

A further group of approximately 144 existing Phase 3 participants 18 years of age and older will be enrolled to receive a third, lower, dose of BNT162b2 of either 5 or 10 µg. Approximately 24 participants 18 to 55 years of age and 48 participants >55 years of age will be enrolled in each dose group.

Three hundred participants 18 to 55 years of age who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19 will be enrolled as a new cohort of participants to receive BNT162b2$_{SA}$ given as a 2-dose series.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 5 µg, 10 µg, 20 µg, 30 µg
- BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S containing South Africa B.1.351 variant–specific mutations): 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated. VE will be demonstrated if the lower bound of the 95% CI for VE is >20%.

In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

The boostability and protection against emerging VOCs for BNT162b2-experienced participants and BNT162b2-naïve participants will be assessed based on GMRs of SARS-CoV-2 SA-neutralizing and/or reference strain–neutralizing titers using a 1.5-fold noninferiority margin and the difference in percentages of participants with seroresponse using a 10% noninferiority margin.

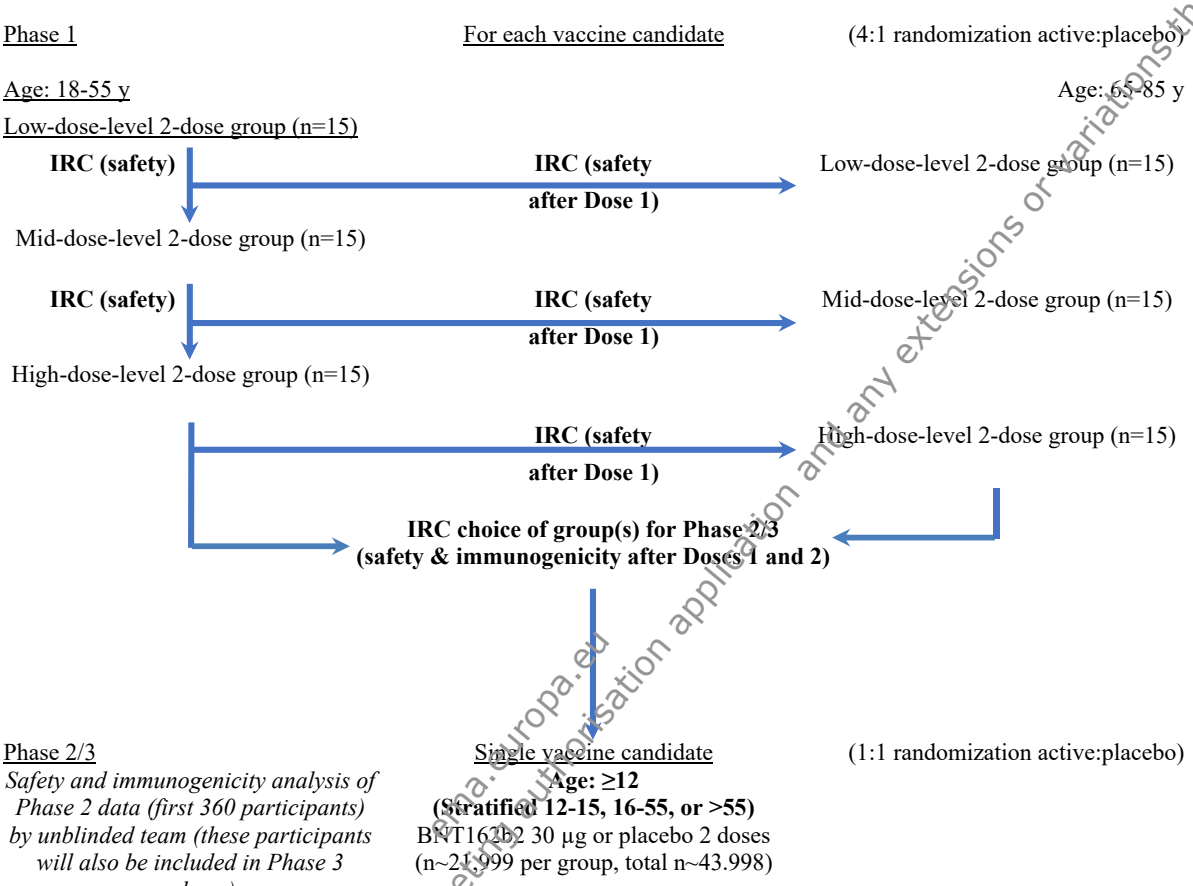
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

Except for the objectives to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age and evaluation of boostability and protection against emerging VOCs by BNT162b2 and BNT162b2$_{SA}$ in Phase 3, the other immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMR, and the associated 95% CIs, for SARS-CoV-2 neutralizing titers, full-length S-binding or S1-binding IgG levels, and/or RBD-binding IgG levels (Phase 1 only) at the various time points.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

1.2. Schema



Abbreviation: IRC = internal review committee.

Note: Participants who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

1.3. Schedule of Activities

The SoA tables provide an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit is required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected. Prior to protocol amendment 16, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b1 or BNT162b2 (at any dose level) will continue in the study as originally planned.

All other participants will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study no later than at the approximate time participants in Phase 2/3 reach Visit 4. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain informed consent	X								*Continued on table below*	
Assign participant number	X									
Obtain demography and medical history data	X									
Obtain details of medications currently taken	X									
Perform physical examination	X	X	X	X	X	X	X			
Measure vital signs (including body temperature)	X	X	X	X	X	X	X			
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL				
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL									
Serological test for prior COVID-19 infection	~20 mL									
Perform urine pregnancy test (if appropriate)	X	X			X					
Obtain nasal (midturbinate) swab(s)[c]		X			X					X
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X		
Confirm eligibility	X	X			X					
Collect prohibited medication use			X	X	X	X	X	X		X

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Review hematology and chemistry results		X		X	X	X	X		*Continued on table below*	
Review temporary delay criteria		X			X					
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X		
Obtain randomization number and study intervention allocation		X								
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL		
Administer study intervention		X			X					
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X								
Provide thermometer and measuring device		X			X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►	◄	———	►			

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7		Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	***Study procedures for Visit 8 onwards continue on the next table***	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X		*Continued on table below*	
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X		X
Collect e-diary or assist the participant to delete application										
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)										X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**		
Obtain informed consent		X					
Confirm participant originally received 10 to 30 µg of BNT162b1 or BNT162b2		X					
Perform urine pregnancy test (if appropriate)		X					
Confirm use of contraceptives (if appropriate)		X	X	X			
Collect prohibited medication use	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X			
Measure body temperature		X					
Confirm eligibility		X					
Review temporary delay criteria		X					
Collect blood sample for immunogenicity assessment	~20 mL	~20 mL	~20 mL	~20 mL	~20 mL	~20 mL	
Obtain nasal (midturbinate) swab(s)		X					X

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**		
Obtain the participant's vaccine vial allocation using the IRT system		X					
Administer 30-µg dose of BNT162b2		X					
Assess acute reactions for at least 30 minutes after study intervention administration		X					
Provide thermometer and measuring device		X					
Remind participant of e-diary technologies		X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		←	→				

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**		
Review ongoing reactogenicity e-diary symptoms and obtain stop dates				X			
Collect AEs and SAEs as appropriate	X	X	X	X	X[b]	X[b]	X
Collect e-diary or assist the participant to delete application						X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: IRT = interactive response technology; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit is required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C. Prior to protocol amendment 16, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b2 or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b2 will continue in the study as originally planned.

All other participants who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4). If they want to receive BNT162b2, they will be unblinded and those who did originally receive placebo will move to the SoA in Section 1.3.3 for their remaining visits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Obtain informed consent	X						
Assign participant number	X						
Obtain demography and medical history data	X						
Perform clinical assessment[c]	X						
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X	
Measure height and weight	X						
Measure temperature (body)	X	X					
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X	X				
Collect nonstudy vaccine information	X	X	X	X			
Collect prohibited medication use		X	X	X	X	X	X
Confirm eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	
Obtain nasal (midturbinate) swab	X	X					X
Obtain randomization number and study intervention allocation	X						
Administer study intervention	X	X					

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X						
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	←	←					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X				
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X
According to eligibility, ascertain willingness to receive BNT162b2 if originally received placebo; if willing, unblind the participant's study intervention assignment (if not already done), and move placebo recipients to the SoA in Section 1.3.3			X	← X			
Collect e-diary or assist the participant to delete application						X	

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. Any placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2.

Visit Number	101	102	103	104	105	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**105 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Confirm participant meets local/national recommending criteria or is at least 175 days after Vaccination 2 (Visit 4/Visit 2)	X					
Obtain informed consent	X					
Confirm participant originally received placebo	X					
Perform urine pregnancy test (if appropriate)	X	X				
Confirm use of contraceptives (if appropriate)	X	X				
Collect prohibited medication use	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	
Review and consider eligibility	X	X				
Review temporary delay criteria	X	X				
Collect blood sample for immunogenicity assessment[c]	~20 mL					
Obtain nasal (midturbinate) swab	X	X				X
Obtain vaccine vial allocation via IRT	X	X				
Administer BNT162b2	X	X				
Assess acute reactions for at least 30 minutes after study intervention administration	X	X				

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Visit Number	101	102	103	104	105	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Collect AEs and SAEs as appropriate	X	X	X	X		X[d]
Contact the participant by telephone			X	X	X	
Request the participant return the e-diary or assist the participant to delete the application					X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)						X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

a. For participants who become eligible according to recommendations detailed separately and available in the electronic study reference portal.
b. For any remaining Phase 2/3 placebo recipients who wish to receive BNT162b2; may be combined with Visit 4 for Phase 2/3 participants.
c. Only if the participant has no blood sample collected in the previous 7 days.
d. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.4. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg)

Select participants in Phase 3 at select sites who originally received 2 doses of BNT162b2 will be offered the opportunity to receive a third (and potentially fourth) dose of BNT162b2 or BNT162b2$_{SA}$.

Visit Number	301	302	303	304	305	306	307	Unplanned
Visit Description	**Vax 3[a]**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**1-Week Follow-up Visit (After Vax 4)[b]**	**1-Month Follow-up Visit (After Vax 4)[b]**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**150 to 210 Days After Visit 2**	**6 to 8 Days After Visit 301**	**28 to 35 Days After Visit 301**	**6 to 8 Days After Visit 303**	**28 to 35 Days After Visit 303**	**175 to 189 Days After Visit 301**	**532 to 560 Days After Visit 301**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			**ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4**				
Obtain informed consent	X							
Confirm participant originally received BNT162b2 at Dose 1 and Dose 2	X							
Perform urine pregnancy test (if appropriate)	X		X[b]					
Confirm use of contraceptives (if appropriate)	X	X	X	X	X			
Collect prohibited medication use	X	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X	X	X		
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X			X	X	
Measure body temperature	X		X[b]					
Confirm eligibility	X		X[b]					
Review temporary delay criteria	X		X[b]					

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application
ema.europa.eu
and any extensions or variations thereof

Visit Number	301	302	303	304	305	306	307	Unplanned
Visit Description	**Vax 3[a]**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**1-Week Follow-up Visit (After Vax 4)[b]**	**1-Month Follow-up Visit (After Vax 4)[b]**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**150 to 210 Days After Visit 2**	**6 to 8 Days After Visit 301**	**28 to 35 Days After Visit 301**	**6 to 8 Days After Visit 303**	**28 to 35 Days After Visit 303**	**175 to 189 Days After Visit 301**	**532 to 560 Days After Visit 301**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			**ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4**				
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation[d]	~120 mL	~120 mL	~120 mL			~120 mL		
Collect blood sample for HLA typing[d]	~5 mL							
Obtain nasal (midturbinate) swab(s)	X		X[b]					X
Obtain randomization number and study intervention allocation using the IRT system	X							
Administer study intervention	X		X[b]					
Assess acute reactions for at least 30 minutes after study intervention administration	X		X[b]					
Provide thermometer and measuring device	X							
Remind participant of e-diary technologies	X		X[b]					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	←	→		↔				

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	301	302	303	304	305	306	307	Unplanned
Visit Description	Vax 3[a]	1-Week Follow-up Visit (After Vax 3)	1-Month Follow-up Visit (After Vax 3)	1-Week Follow-up Visit (After Vax 4)[b]	1-Month Follow-up Visit (After Vax 4)[b]	6-Month Follow-up Visit	18-Month Follow-up Visit	Potential COVID-19 Illness Visit[c]
Visit Window (Days)	150 to 210 Days After Visit 2	6 to 8 Days After Visit 301	28 to 35 Days After Visit 301	6 to 8 Days After Visit 303	28 to 35 Days After Visit 303	175 to 189 Days After Visit 301	532 to 560 Days After Visit 301	Optimally Within 3 Days After Potential COVID-19 Illness Onset
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4				
Review ongoing reactogenicity e-diary symptoms and obtain stop dates			X		X			
Collect AEs and SAEs as appropriate	X	X	X	X	X	X[e]	X[e]	X
Collect e-diary or assist the participant to delete application							X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)								X

Abbreviations: e-diary = electronic diary; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; vax = vaccination.

a. Visit 301 can occur on the same day as Visit 4, but all procedures for both visits must be conducted (including collection of all blood samples).
b. Only for those participants who will receive Dose 4.
c. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
d. Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants who will receive a third (but not fourth) dose of BNT162b2 at 30 µg or $BNT162b2_{SA}$ at select sites only.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.5. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants

As part of Amendment 14, an additional cohort of BNT162b2-naïve participants will be enrolled to receive BNT162b2$_{SA}$ per the following SoA.

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain informed consent	X						
Assign participant number	X						
Obtain demography and medical history data	X						
Perform clinical assessment[c]	X						
Measure height and weight	X						
Measure temperature (body)	X	X					
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X	X	X			
Collect nonstudy vaccine information	X	X	X	X	X		
Collect prohibited medication use		X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X			X	X	X	
Confirm eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment	~50 mL		~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation[d]	~120 mL		~120 mL	~120 mL	~120 mL		
Collect blood sample for HLA typing[d]	~5 mL						

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain nasal (midturbinate) swab	X	X					X
Obtain the participant's vaccine vial allocation using the IRT system	X	X					
Administer BNT162b2$_{SA}$	X	X					
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X						
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	◄►	◄►					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X		X			
Collect AEs and SAEs as appropriate	X	X	X	X	X[e]	X[e]	X
Collect e-diary or assist the participant to delete application						X	

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: e-diary = electronic diary; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; vax = vaccination.

a. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
b. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
c. Including, if indicated, a physical examination.
d. Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants at select sites only.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

1.3.6. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4 or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

Visit Number	201	202 Onward
Visit Description	**Asymptomatic SARS-CoV-2 Infection Surveillance Consent**	**Asymptomatic SARS-CoV-2 Infection Surveillance Swab**
Visit Window (Days)	**From Approval of Protocol Amendment 11**	**Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection**
Obtain informed consent for asymptomatic SARS-CoV-2 infection surveillance	X	
Collect prohibited medication use	X	
Collect blood sample for immunogenicity assessment[a]	~20 mL/~10 mL	
Obtain nasal (midturbinate) swab (self-swab at home or by site staff at an in-person visit)	X	X
Collect AEs and SAEs as appropriate[b]	X	

a. Only if the participant has no blood sample collected in the previous 7 days. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
b. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no licensed vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

As more data about COVID-19 continue to accrue, the potential duration of protection afforded after a wild-type SARS-CoV-2 infection, and by vaccination, remains unknown. In addition, mutated SARS-CoV-2 VOCs have started to emerge, for example in the UK (known as 20I/501Y.V1, VOC 202012/01, or B.1.1.7), SA (known as 20H/501Y.V2 or B.1.351), and Brazil (known as P.1).[4]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[5,6]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may

be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Three SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 3 antigens:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5);

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9);

- **BNT162b2s01** (variant RBP020.11): nucleoside-modified messenger RNA (modRNA) as above, but encoding the P2 S containing South Africa B.1.351 variant–specific mutations, hereafter referred to as BNT162b2$_{SA}$, as a representative variant of concern (VOC).

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

In light of the unknowns regarding duration of protection, as well as the emerging VOCs, it is important to understand the boostability of BNT162, and potential heterologous protection against emerging VOC(s). A first step to address this will be to study an additional dose of BNT162b2 at 30 µg given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ (based upon the South African variant and hereafter referred to as BNT162b2$_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

This document can only be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[7] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[8] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with the currently available therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.

- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.

- All participants 12 to 15 years of age will be included in the reactogenicity subset (see Section 8.2.2).

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support a marketing authorisation application or any extensions or variations thereof
ema.europa.eu

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[9]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of an efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	• GMCs/GMTs at the time of Dose 3 and 7 days and 1 month after Dose 3. • GMFRs from before Dose 3 to 7 days and 1 month after Dose 3	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels
	• GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers
	• GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives	Estimands	Endpoints
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Objectives[a]	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants, or as 2 doses to BNT162b2-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2-experienced participants	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 5 or 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary Immunogenicity ***BNT162b2-experienced participants***		
To demonstrate the noninferiority of the anti–reference strain immune response after a third dose of BNT162b2 at 30 µg compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
BNT162b2-naïve participants		
To demonstrate the noninferiority of the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
BNT162b2-experienced participants		
To demonstrate the noninferiority of the anti-SA immune response after a third dose of BNT162b2 at 30 µg compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Objectives[a]	Estimands	Endpoints
To demonstrate the noninferiority of the anti–reference strain immune response after 1 dose of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ and a third dose of BNT162b2 at 30 µg	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg	SARS-CoV-2 SA NT in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$ or the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ and the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate a statistically greater anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 SA NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
To descriptively compare the anti–reference strain immune response after 2 doses of BNT162b2$_{SA}$ and after 2 doses of BNT162b2	GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Objectives[a]	Estimands	Endpoints
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization	In participants who received BNT162b2 at initial randomization: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate and characterize the SARS-CoV-2 isolate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers • Identification of SARS-CoV-2 variant(s)
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers
To describe the immune response to any VOCs not already specified	Geometric mean NT for any VOCs not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2	• SARS-CoV-2 NTs for any VOCs not already specified
To describe the immune response to a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$	• GMTs at Dose 3 and subsequent time points • GMFRs from Dose 3 to subsequent time points	• SARS-CoV-2 reference strain NTs
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and SA in a subset of participants: • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 2 doses to BNT162b2-naïve participants • 7 Days and 1 and 6 months after BNT162b2 given as a third dose to BNT162b2-experienced participants		

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for description of the manufacturing process.

Up until the final efficacy analysis, this protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ at 30 µg (based upon the South African variant and hereafter referred to as

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

$BNT162b2_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive $BNT162b2_{SA}$ given as a 2-dose series, separated by 21 days.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than at the approximate time participants in Phase 2/3 reach Visit 4.

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162.

Participants are expected to participate for up to a maximum of approximately 26 months.

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 280 participants from each of the 2 age groups (12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

For evaluation of boostability and protection against emerging VOCs, 600 existing Phase 3 participants 18 to 55 years of age will be rerandomized in a 1:1 ratio to receive either a third dose of BNT162b2 at 30 µg or a third dose of BNT162b2$_{SA}$.

A further group of approximately 144 existing Phase 3 participants 18 years of age and older will be enrolled to receive a third, lower, dose of BNT162b2 of either 5 or 10 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Approximately 24 participants 18 to 55 years of age and 48 participants >55 years of age will be enrolled in each dose group. An additional group of 30 existing Phase 3 participants 18 to 55 years of age will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$. For these 30 participants, through 1 month after their first dose of BNT162b2$_{SA}$ the participant will be blinded to their vaccine allocation but the investigator and Sponsor will not be. Serum samples from these participants may be used for assay development purposes and, except for objectives relating to response to a fourth dose, their results will be analyzed separately from the main immunogenicity analyses.

Three hundred participants 18 to 55 years of age who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19 will be enrolled as a new cohort of participants to receive BNT162b2$_{SA}$ given as a 2-dose series.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 2/3 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4).

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

The changes to the protocol as part of protocol amendment 14 to assess boostability and homologous/heterologous protection against emerging VOCs allow the evaluation of safety and immunogenicity of BNT162b2$_{SA}$:

- When given as a third dose to C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously (ie, BNT162b2-experienced) and have not experienced COVID-19.
- In a small separate group of individuals who previously received 2 doses of BNT162b2 followed by 1 dose of BNT162b2$_{SA}$, a second BNT162b2$_{SA}$ dose will also be given 1 month after Dose 1 of BNT162b2$_{SA}$.
- When given as a 2-dose series, separated by 21 days, in newly recruited participants who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

In addition, a group of C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously will receive a third dose of BNT162b2.

This approach will allow an evaluation of immunogenicity against the reference ancestral SARS-CoV-2 strain (Wuhan-Hu-1/USA-WA1) and the selected South African VOC using a noninferiority approach based on neutralizing antibody titers in prior BNT162b2 vaccinees who receive either a homologous boost (with BNT162b2) or a heterologous boost (with BNT162b2$_{SA}$), as well as new vaccinees receiving 2 doses of BNT162b2$_{SA}$.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.6. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness visit will occur and, prior to protocol amendment 16, a subsequent convalescent visit would occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization.

   For the boostability and protection-against-VOCs subset:

   - Existing participants enrolled to receive a third dose of BNT162b2 at 30 µg or BNT162b2$_{SA}$; male or female participants between the ages of 18 and 55 years, inclusive, at rerandomization.
   - Newly enrolled participants enrolled to receive 2 doses of BNT162b2$_{SA}$; male or female participants between the ages of 18 and 55 years, inclusive, at enrollment.
   - Existing participants enrolled to receive a third dose of BNT162b2 at 5 or 10 µg; male or female participants ≥18 years at rerandomization.

   Note that participants <18 years of age cannot be enrolled in the EU.

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

5. **Boostability and protection-against-VOCs existing participant subset only:** Participants who provided a serum sample at Visit 3, with Visit 3 occurring within the protocol-specified window.

Informed Consent:

6. Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Chronic pulmonary disease
- Asthma
- Current vaping or smoking
- History of chronic smoking within the prior year
- Chronic liver disease
- Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
- Resident in a long-term facility
- BMI >30 kg/m^2
- Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry through and including 6 months after the last dose of study intervention, with the exception of non-Pfizer interventional studies for prevention of COVID-19, which are prohibited throughout study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Sore throat;
- Diarrhea;
- Vomiting.

2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.

3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 3 investigational RNA vaccine candidates, with the addition of saline placebo, are the 4 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 5 µg, 10 µg, 20 µg, 30 µg
- BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S containing South Africa B.1.351 variant–specific mutations): 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	5-, 10-, 20-, 30-µg	30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. Participants who originally received placebo and accept the offer to receive BNT162b2 at defined points as part of the study will receive 1 dose of BNT162b2 at each additional vaccination visit (Visits 101 and 102) in accordance with the study's additional SoA (Section 1.3.3). The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162 at Visit 8a.

Participants in the subset for evaluation of boostability and protection against emerging VOCs will receive either a third dose of BNT162b2 or BNT162b2$_{SA}$ approximately 5 to 7 months after their second dose of BNT162 at Visit 301. Of those who receive BNT162b2$_{SA}$ at Visit 301, a subset will receive a further dose of BNT162b2$_{SA}$ at Visit 303.

BNT162b2-naïve participants who are enrolled under protocol amendment 14 to receive BNT162b2$_{SA}$ will receive 1 dose of study intervention at each vaccination visit, Visits 401 and 402.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

9. Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

To allow administration of BNT162b2 to participants who originally received placebo, site staff will be unblinded to individual participants' original study intervention allocation as the participants become eligible for vaccination under local/national recommendations or from 6 months after the second dose.

For the group of 30 existing Phase 3 participants 18 to 55 years of age who will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the investigator will not be.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).

- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.

- An unblinded team supporting interactions with and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

- After the formal data release of the final efficacy analysis of at least 164 cases, which is considered the primary completion of the study efficacy objectives, additional statisticians and programmers will become unblinded at the participant level to prepare unblinded analyses and other regulatory activities. A group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study.

- After the study data used for submission become public, the blinded study team will also have access to those data, and become unblinded at a group level.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- When a participant is unblinded for potential receipt of BNT162b2 (if he or she originally received placebo) per Section 8.16, the study team will become unblinded to the participant's original study intervention allocation.

For the group of 30 existing Phase 3 participants 18 to 55 years of age who will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the sponsor will not be.

The study will be unblinded in stages once all ongoing participants either have been individually unblinded or have concluded their 6-month post–Dose 2 study visit, as follows:

- Phase 1 (after Visit 8).
- Phase 2/3, ≥16 years (after Visit 4).
- Phase 3, 12 to 15 years (after Visit 4).
- Original Phase 3 participants rerandomized to assess boostability and protection against emerging VOCs (after Visit 306).

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

Instructions on how to unblind participants ahead of administration of BNT162b2 to placebo recipients, or for other, nonemergency reasons, will be provided separately: this unblinding will NOT be performed in the IRT. The date (that the participant becomes aware of study intervention allocation) and reason that the blind was broken must be recorded in the source documentation and CRF.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants). In addition, for Phase 1 participants who go on to receive a third dose of BNT162, concomitant vaccinations will be collected from the time the participant provides informed consent (for receipt of Vaccination 3) through and including Visit 8c (1 month after the third dose). For BNT162-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to the time the participant provides informed consent (for participation in the subset) through and including Visit 306. For BNT162b2-naïve participants, the subset for evaluation of protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to study enrollment through and including Visit 405.
    - Nonstudy coronavirus vaccines are listed in Section 6.5.1 as prohibited throughout the study and should therefore be recorded at any time they are given during study participation. This includes blinded BNT162b2 vaccine/placebo given in the B7471026 study.
- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.
- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 and from 28 days prior to Visit 8a to Visit 8c for Phase 1 participants, and from 28 days prior to enrollment to Visit 3 for Phase 2/3 participants). Use is also prohibited for participants in the subset for evaluation of boostability and protection against emerging VOCs, from 28 days prior to Visit 301 to Visit 303/305 and the BNT162b2-naïve participants from 28 days prior to enrollment to Visit 404.

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, for whatever reason, a participant receives only 1 dose of BNT162b2, the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. For example, because of a medication error a participant receives only 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa); the participant can return at a later date for the unscheduled visit. In this situation:

- Obtain informed consent.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s).

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

Note: Participants who are randomized in the C4591031 study should be withdrawn from this study.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

If a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately up to: 500 mL for participants in Phase 1, 110 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum.

Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 670 mL during the 24-month study period.

For those Phase 3 participants enrolled in the subset to receive an additional dose of BNT162b2 or BNT162b2$_{SA}$, the total blood sampling volume for individual participants in this study is approximately up to 310 mL for those who receive 3 doses and 410 mL for those

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

who receive 4 doses. Those participants in the subset who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of approximately up to 795 mL.

For those participants enrolled into the additional cohort (added as part of protocol amendment 14) of BNT162b2-naïve participants who will receive 2 doses of BNT162b2$_{SA}$, the total blood sampling volume for individual participants is approximately up to 250 mL. Those participants in the cohort who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of approximately up to 735 mL.

For all participants, other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

8.1.1. Efficacy Against COVID-19

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[10] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid, FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction*;
  - Admission to an ICU;

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

8.1.2. Efficacy Against Asymptomatic SARS-CoV-2 Infection

VE against asymptomatic SARS-CoV-2 infection will be evaluated in 2 ways, through impact on seroconversion of N-binding antibody and impact on NAAT-confirmed SARS-CoV-2 infection, in originally enrolled Phase 2/3 participants not suffering from COVID-19. Data from participants who receive more than 2 doses of BNT162b2 will not be included after they receive a third dose.

8.1.2.1. Seroconversion of N-Binding Antibody

Blood samples for assessment of N-binding antibodies are drawn at multiple scheduled visits. An asymptomatic case of SARS-CoV-2 infection based on seroconversion of N-binding antibody is defined as positive N-binding antibody at a post–Dose 2 visit in participants without serological evidence of infection (determined by negative N-binding antibody) at Visit 1 or virological evidence of infection (determined by negative NAAT result at Visit 1 and Visit 2 and at the time of a potential COVID-19 illness). The requirement for a negative NAAT result at Visit 2 is to focus on assessment of protection against asymptomatic infection after 2 doses of vaccine, to the extent possible in an analysis based on seroconversion of N-binding antibody, recognizing that it is not possible to identify and exclude all asymptomatic infections that occur after Dose 1 and prior to Dose 2.

A secondary definition will be applied without the requirement for a negative NAAT result at Visit 2 to allow assessment of protection after 1 dose of vaccine. A positive N-binding antibody at a postvaccination visit in participants with negative N-binding antibody at Visit 1 and negative NAAT results at Visit 1 and at the time of a potential COVID-19 illness is considered an asymptomatic case.

8.1.2.2. NAAT-Confirmed SARS-CoV-2 Infection

For participants who consent to participate in an intensive period of surveillance, nasal swabs will be obtained to assess SARS-CoV-2 infection by NAAT (see Section 8.1.5).

An asymptomatic case of NAAT-confirmed SARS-CoV-2 infection is defined as a positive NAAT result on a nasal swab collected during the surveillance period from participants without COVID-19 symptoms at the time the nasal swab was taken, or within 14 days after

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

it. The onset date of the asymptomatic case is the collection date of the first nasal swab that tested positive.

8.1.3. Vaccine-Induced Immunogenicity

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay (reference strain and SA variant)
- Full-length S-binding or S1-binding IgG level assay
- RBD-binding IgG level assay (Phase 1 only)

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

Additional whole blood samples of ~120 mL will be obtained from a group of up to approximately 30 participants in each 30-µg group in the subset for evaluation of boostability and protection against emerging VOCs (both BNT162b2-experienced and BNT162b2-naïve) at select sites for isolation of PBMCs. These samples will be used to describe T-cell responses to emerging VOCs and reference strains. Some of the sample may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs, for understanding the B-cell, T-cell, and antibody repertoires. A blood sample of ~5 mL for HLA typing will also be obtained. Some of the 5-mL blood sample collected for HLA typing may be used for DNA and/or RNA isolation to further characterize HLA type.

8.1.4. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine related assay work supporting vaccine programs. No testing of the participant's DNA will be performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

8.1.5. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.6.

The nasal swabs will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2. For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with Section 8.3.2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Certain participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. In addition, participants 16 through 17 years of age enrolled under protocol amendment 9 and onwards will be included in the reactogenicity subset. All other participants, including those who originally received placebo and then received BNT162b2 under protocol amendment 10 and onwards, will not complete a reactogenicity e-diary but will have their local reactions and systemic events detected and reported as AEs in accordance with Section 8.3.2. Phase 1 participants who receive a third dose of BNT162b2 will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage in the reactogenicity e-diary for 7 days following administration of the study intervention. Participants in the subset for evaluation of boostability and protection against emerging VOCs (both BNT162b2-experienced and BNT162b2-naïve) will be asked to monitor and record local reactions, systemic events, and antipyretic medication use in the reactogenicity e-diary for 7 days following each administration of the study intervention.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[9]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the administration of the second dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

Administration of BNT162b2 at Visits 101 and 102 to pregnant participants who originally received placebo and choose to be unblinded and receive BNT162b2 may be considered if there are local or national recommendations for COVID-19 vaccination of pregnant women, and the investigator and participant are in agreement. This overrides the requirements stated in the previous paragraph, and will not be considered as a protocol deviation. However, the EDP should still be reported in accordance with Section 8.3.5.1.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Additionally, for those participants who originally received placebo but go on to receive BNT162b2 at Vaccinations 3 and 4, AEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) through and including Visit 103. SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) to approximately 6 months after the second dose of BNT162b2 (Visit 104).

For Phase 1 participants who go on to receive a third dose of BNT162, AEs and SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccination 3) through and including Visit 8c (1 month after the third dose).

For BNT162b2-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, AEs will be collected from the time the participant provides informed consent (for participation in the subset) through and including Visit 303 for those receiving 1 additional dose and Visit 305 for those who receive 2 additional doses. For both schedules, this equates to collection for up to 1 month after the last dose. SAEs will be collected from the time the participant provides informed consent (for participation in the subset) through and including Visit 306 (5 or 6 months after the last dose, depending upon group).

For BNT162b2-naïve participants, the subset for evaluation of protection against emerging VOCs, AEs will be collected from the time the participant provides informed consent through and including Visit 404 (1 month after the second dose). SAEs will be collected from the time the participant provides informed consent through and including Visit 405 (6 months after the second dose).

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:

  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.

  - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose of study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu/

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.6. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.6.1. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

8.3.7. Cardiovascular and Death Events

Not applicable.

8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.9. Adverse Events of Special Interest

Not applicable.

8.3.9.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.3.10. Medical Device Deficiencies

Not applicable.

8.3.11. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Some of the blood samples collected for PBMC isolation and HLA typing may be used for DNA and/or RNA isolation. The DNA and/or RNA samples from the PBMC isolation may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs, for understanding the B-cell, T-cell, and antibody repertoires. The DNA and/or RNA samples from the blood sample for HLA typing may be used to further characterize HLA type.

See Appendix 9 for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

Unless stated otherwise, all study visits are intended to be conducted in person at the study site. If this is not possible, because of local circumstances related to the COVID-19 pandemic, study procedures that do not require in-person participant contact may be performed by telehealth. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Irrespective of the nature of the contact, all visit procedures are expected to be performed on the same day.

As the protocol design includes visits of an unplanned nature, multiple visits may occur on the same day, but all procedures for all visits must be conducted (including collection of all blood samples).

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof are the european agency

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 100 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

8.11.1.10. Between Visits 8 and 9

All participants who have not already been unblinded, no later than at the approximate time participants in Phase 2/3 reach Visit 4, will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, he or she will move to the procedures in Section 8.16.

8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of a third dose of BNT162, his or her next visit should be Visit 9.

- Confirm that the participant originally received 10-µg, 20-µg, or 30-µg doses of BNT162b1 or BNT162b2 at Vaccinations 1 and 2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Record nonstudy vaccinations as described in Section 6.5.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 2, 3, and 6 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Site staff member(s) will dispense/administer a 30-µg dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.

- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

    - Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

    - Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):

        - Fever ≥39.0°C (≥102.1°F)

        - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)

        - Severe pain at the injection site

        - Any severe systemic event

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.

This document can only be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- If Visit 3 is being conducted under amendment 12 onward: If the participant is eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, determine if he/she is willing to receive BNT162b2 as part of the study. If so, unblind the participant's study intervention assignment, and move placebo recipients to the procedures in Section 8.16.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- If not already unblinded, unblind the participant's study intervention assignment, and move placebo recipients willing to receive BNT162b2 to the procedures in Section 8.16.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;

- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination (either as part of this study, co-enrolled C459 studies, or the B7471026 [20vPnC] study), potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;

- Fever;

- New or increased cough;

- New or increased shortness of breath;

- Chills;

This document cannot be used to support any marketing authorization application and any extensions or variations thereof

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
  - Symptoms and signs, including
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
    - Significant acute renal, hepatic, or neurologic dysfunction

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

- Clinical diagnosis
- Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.
- Full blood count
- Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
- Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
- Number and type of any healthcare contact; duration of hospitalization and ICU stay
- Death

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

Prior to protocol amendment 16, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol; however, data collected from convalescent visits that occurred prior to protocol amendment 16 will remain part of the study data set.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).

- An alert in the event that the participant is hospitalized.

- Visit reminders.

- Messages of thanks and encouragement from the study team.

- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

8.15. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 or 14 days after receipt of the second dose, depending on the objective) of past SARS-CoV-2 infection.

- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

- Asymptomatic SARS-CoV-2 infection surveillance visits: To determine the incidence of asymptomatic SARS-CoV-2 infection.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, asymptomatic SARS-CoV-2 infection surveillance visit swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result, either asymptomatic or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result), prior to Visit 2 should receive Vaccination 2 as normal.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

If a participant becomes eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study.

Placebo recipients who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Dose 2, and will follow the procedures listed in this section for the remainder of their participation in the study. For Phase 2/3 participants, Visit 101 could occur at the same time as the original Visit 4.

8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant originally received only placebo at Vaccination 1/2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 4 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101)

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Record AEs as described in Section 8.3.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record AEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 103 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 104 (if any).
- Request the return of the participant's e-diary or assist the participant/participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Inform the participant/participant's parent(s)/legal guardian that his or her study participation has ended.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg)

The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 or a third and potentially a fourth dose of prototype BNT162b2$_{SA}$.

8.17.1. Visit 301 – Vaccination 3: (150 to 210 Days After Visit 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of a third dose of BNT162b2, he or should remain on the Phase 2/3 visit schedule.

Note: This visit can occur on the same day as Visit 4, but all procedures for both visits must be conducted (including collection of all blood samples).

- Confirm that the participant originally received BNT162b2 at Vaccinations 1 and 2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Record nonstudy vaccinations as described in Section 6.5.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 1, 2, 3, 5, and 6 are met and exclusion criteria 1, 3, 5, 8, 10, 11, 12, 13, 15, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. **The IRT system will also assign an additional single participant number; this number will not be used as the primary identifier for the participant, but must be included in the participant's source documents and transcribed into the CRF**. The system will also identify those participants who are to receive a fourth dose; this should be kept blinded until from the participant until Visit 303.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):

  - Fever ≥39.0°C (≥102.1°F)

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)

  - Severe pain at the injection site

  - Any severe systemic event

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.17.2. Visit 302 – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 301)

- Record AEs as described in Section 8.3.

- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.3. Visit 303 – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 301)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.

Only if the participant is to receive a further dose of BNT162b2$_{SA}$:

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 1, 2, 3, 5, and 6 are met and exclusion criteria 1, 3, 5, 8, 10, 11, 12, 13, 15, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):
  - Fever ≥39.0°C (≥102.1°F)
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)
  - Severe pain at the injection site
  - Any severe systemic event
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc europaea

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.4. Visit 304 – 1-Week Follow-up Visit (Vaccination 4): (6 to 8 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2SA

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.5. Visit 305 – 1-Month Follow-up Visit (Vaccination 4): (28 to 35 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2SA

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.6. Visit 306 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 301):

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.17.7. Visit 307 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 301):

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record latest CD4 count and HIV viral load.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.18. Administration of BNT162b2$_{SA}$ to BNT162b2-naïve Participants

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

8.18.1. Visit 401 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Obtain any medical history of clinical significance.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - Provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
    - Severe pain at the injection site.
    - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the study intervention accountability records.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.18.2. Visit 402 – Vaccination 2: (19 to 23 Days After Visit 401)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the study intervention accountability records.

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.18.3. Visit 403 – 1-Week Follow-up Visit (After Vaccination 2): (6 to 8 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.18.4. Visit 404 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.18.5. Visit 405 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

8.18.6. Visit 406 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 402)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.19. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11 until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The surveillance will be conducted per the procedures listed below.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

8.19.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11

Before surveillance begins and any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The visit should be conducted only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1) and this visit should be temporarily delayed until the symptoms have resolved.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 3 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Record AEs as described in Section 8.3 (only if the participant remains in the AE reporting period; see Section 8.3.1).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Ask the participant to obtain a surveillance self-swab at home in approximately 14 days or schedule an appointment for the participant to return to collect the swab at the site. The swab should be collected only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.19.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection

This is a repeating swab collection and will be conducted approximately every 14 days until the intensive surveillance period ends.

- Participant collects a self-swab and ships it to the site for assessment at the central laboratory. The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- Complete the source documents with the swab information.

- The investigator or an authorized designee completes the CRFs with the swab information.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by all-available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either VE_1 >30% or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated based on the lower bound of the 95% CI. VE will be demonstrated if the lower bound of the 2-sided 95% CI for VE is >20%.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

9.1.2.2.1. Hypothesis for Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2**.** If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

9.1.2.2.2. Hypotheses for Boostability and Protection Against Emerging SARS-CoV-2 VOCs

The primary and secondary objectives for boostability and protection against emerging VOCs for BNT162b2-experienced participants and BNT162b2-naïve participants will be assessed based on:

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- GMRs of SARS-CoV-2 SA and/or reference strain neutralizing titers using a 1.5-fold noninferiority margin. Noninferiority is met if the lower limit of the alpha adjusted CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.8.

- The difference in percentages of participants with seroresponse to SA and/or reference strain using a 10% noninferiority margin. Noninferiority is met if the lower limit of the alpha-adjusted CI for the difference in percentages of participants with seroresponse is >-10%.

Seroresponse is defined as achieving ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

9.1.2.2.2.1. Multiplicity Control for the Boostability and Protection-Against-VOCs Objectives

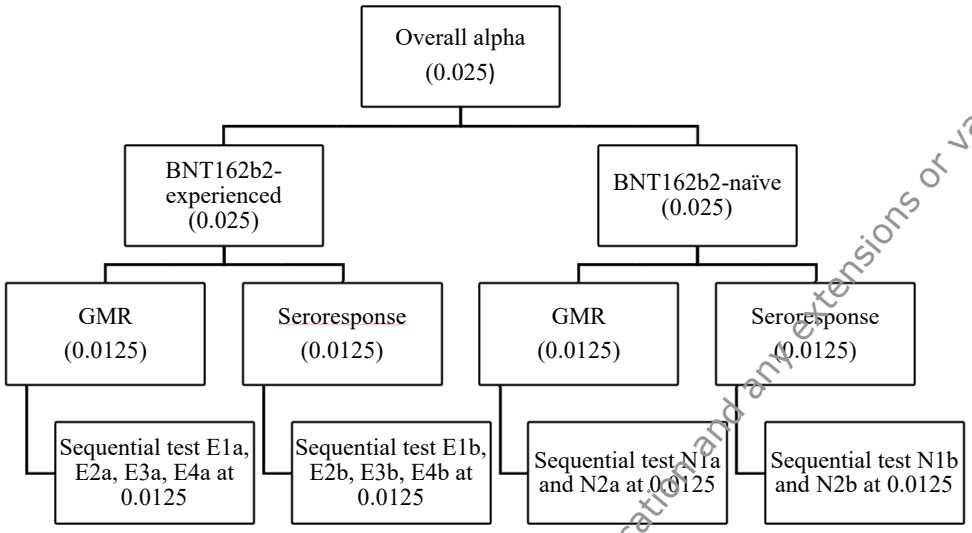
Figure 1 outlines the type I error control strategy for multiple objectives across different populations (BNT162b2-experienced or BNT162b2-naïve) and estimands (GMR or seroresponse).

The objectives for BNT162b2-experienced participants and BNT162b2-naïve participants will be evaluated independently. The vaccine-experienced and -naïve individuals are different populations with different objectives. The 2 populations are included in the same study to improve operational efficiency. Therefore, no type I error adjustments will be applied to the assessments of the 2 populations.

For each population, the objectives will be evaluated separately for each estimand. To control the overall type I error, the 1-sided alpha of 0.025 will be split and allocated equally to each estimand. Specifically, for each estimand, the hypotheses will be tested in sequential order (as listed in the objectives in Section 3) using a 1-sided alpha of 0.0125 (Figure 1, where E and N represent vaccine-experienced and vaccine-naïve, respectively, and a and b represent GMR and seroresponse estimands, respectively).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Figure 1. Multiplicity Schema



9.2. Sample Size Determination

9.2.1. Phase 1

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

9.2.2. Efficacy Against COVID-19

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

9.2.3. Efficacy Against Asymptomatic Infection

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection will be assessed in Phase 2/3 participants (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT). Assuming a true VE of 70%, a total of 53 asymptomatic cases will provide approximately 90% power to conclude true VE >20%. A total of 206 cases is needed to have 90% power if the true VE is 50%. The hypothesis for asymptomatic seroconversion of N-binding antibody will be tested if at least 206 cases are accrued. The hypothesis for asymptomatic infection based on central laboratory–confirmed NAAT in participants who are consented to participate in the intensive surveillance phase will be tested if at least 53 cases are accrued.

9.2.4. Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 280 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.65	-0.2	225	90.4%

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer.
a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).
b. At 0.05 alpha level (2-sided).

9.2.5. Boostability and Protection Against Emerging SARS-CoV-2 VOCs

To assess boostability and protection against emerging SARS-CoV-2 VOCs, approximately 300 participants will be enrolled in each of the 3 groups (BNT162b2-experienced participants to receive either a third dose of BNT162b2 at 30 µg [Group 1] or a third dose of BNT162b2$_{SA}$ [Group 2], BNT162b2-naïve participants to receive 2 doses of BNT162b2$_{SA}$ [Group 3]) to provide an acceptable safety database.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Assuming 20% nonevaluable rate, approximately 240 evaluable participants in each group will contribute to immunogenicity evaluation. This will provide sufficient power for noninferiority evaluations with appropriate multiplicity adjustment for type I error control.

For comparisons based on GMR, the assay standard deviation in log scale is assumed to be 0.74 based on results from Phase 2 of the study and adjusted for assay variability. A GMR of 1 is assumed for each comparison.

For comparisons based on seroresponse, a 90% response rate is assumed for each comparative group or at each comparative time point.

Within-Group Comparison for BNT162b2-Experienced Participants

For each randomized group of BNT162b2-experienced participants (Group 1: received a third dose of BNT162b2 at 30 μg and Group 2: received a third dose of $BNT162b2_{SA}$), with 240 evaluable participants and the stated assumptions for the GMR and standard deviation, the study has >99.9% power to demonstrate NI based on GMR for the objectives in vaccine-experienced individuals using a 1.5-fold margin.

Assuming true response rate of 90% at each time point and 10% of the participants having a different response status at 2 comparative timepoints, the study has 99% power to show NI based on seroresponse rate for the objectives in vaccine-experienced individuals using a 10% margin. The study will have 89% power to show NI if 20% of the participants have a different response status at 2 comparative timepoints.

Between-Group Comparison of BNT162b2-Naïve Participants to Selected Existing Phase 3 Participants Who Received 2 Doses of BNT162b2

Approximately 300 participants will be selected from the existing Phase 3 participants who received 2 doses of BNT162b2 to form the control group for the BNT162b2-naïve participants. The selection will ensure comparable distribution of age, sex, and other demographic factors in the control group and BNT162b2-naïve group. With 240 evaluable BNT162b2-naïve participants and 240 evaluable participants in the control group and the above stated assumptions for the GMR, standard deviation, and seroresponse rate, the study has >99.9%% power to declare NI based on GMR for the objectives in vaccine-naïve individuals using a 1.5-fold margin and 89.7% power to declare NI based on seroresponse rate using a 10% margin.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

9.2.6. Safety

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=300	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.03	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.06	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.11	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.16	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.21	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.26	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.36	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.45	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.53	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.59	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.65	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.78	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	0.95	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 3 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 (or BNT162b1 for Phase 1) as initially randomized, with Dose 2 received within the predefined window, receive a third dose of BNT162b2 or BNT162b2$_{SA}$ as rerandomized (or receive a third dose of BNT162b2 for Phase 1), have at least 1 valid and determinate immunogenicity result after Dose 3 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 4 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 as initially randomized, with Dose 2 received within the predefined window, receive 2 booster doses of BNT162b2$_{SA}$ as rerandomized, have at least 1 valid and determinate immunogenicity result after Dose 4 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emea-eropean
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Population	Description
Dose 3 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 (or BNT162b1 for Phase 1) at initial randomization, receive a third dose of BNT162b2 or BNT162b2$_{SA}$ at rerandomization (or receive a third dose of BNT162b2 for Phase 1), and have at least 1 valid and determinate immunogenicity result after Dose 3.
Dose 4 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 at initial randomization, receive 2 booster doses of BNT162b2$_{SA}$ at rerandomization, and have at least 1 valid and determinate immunogenicity result after Dose 4.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
Evaluable efficacy (seroconversion)	All eligible randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window, have at least 1 N-binding antibody test result available at a post–Dose 2 visit, and have no other important protocol deviations as determined by the clinician prior to the first post–Dose 2 N-binding antibody test.
Evaluable efficacy (asymptomatic surveillance)	All eligible randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window, consent to participate in the asymptomatic surveillance, and have no other important protocol deviations as determined by the clinician on or before the start of the asymptomatic surveillance period.
All-available efficacy	Dose 1 all-available: All randomized participants who receive at least 1 vaccination. Dose 2 all-available: All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention. Analyses of reactogenicity endpoints will be based on a subset of the safety population that includes participants with any e-diary data reported after vaccination.
Booster safety	All participants who receive at least 1 booster dose of the study intervention.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Empirical RCDCs will be provided for all immunogenicity analyses.

Endpoint	Statistical Analysis Methods
Primary immunogenicity (Phase 3, boostability and protection against emerging VOCs)	In order to allow direct comparability with the reference strain, the anti-SA NTs may be adjusted to account for intrinsic variant or assay characteristics. The small group of existing Phase 3 participants who are to receive a third and fourth dose of BNT162b2$_{SA}$ will not be included in the primary and secondary analyses except for the last secondary descriptive objective. ***<u>BNT162b2-Experienced Participants:</u>*** **E1a: GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 in the same individuals** **E2a: GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** The comparisons of different NTs (anti-SA or anti–reference strain) or the same NTs at different time points within the same group will be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Endpoint	Statistical Analysis Methods
	limited to participants with nonmissing values at both time points or both NT measurements. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (eg, later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 97.5% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. Noninferiority of E1a and E2a will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8. **E1b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2 in the same individuals** **E2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** Similar to E1a and E2a, the within-group comparisons of seroresponse to different NTs (anti-SA or anti–reference strain) or the same NTs at different time points within the same group will be limited to participants with nonmissing values at both time points or both NT measurements. The percentages of participants with seroresponse at each time point and the difference in percentages will be provided. The 2-sided 97.5% CIs for the difference in percentages of participants with seroresponse will be calculated using the adjusted Wald interval as described by Agresti and Min (2005)[11] for comparing matched proportions. Noninferiority of E1b and E2b will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%. ***BNT162b2-Naïve Participants:*** **N1a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Endpoint	Statistical Analysis Methods
	For the between-group comparison, GMRs will be calculated as the mean of the difference of logarithmically transformed assay results between 2 groups and exponentiating the mean. The associated 2-sided 97.5% CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed titers and exponentiating the confidence limits. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8. **N1b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2** The difference in percentages of participants with seroresponse and associated 2-sided 97.5% CIs will be calculated using the Miettinen and Nurminen method.[12] Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%.
Secondary immunogenicity (Phase 3, boostability and protection against emerging VOCs)	***BNT162b2-Experienced Participants:*** **E3a: GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** **E4a: GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 in the same individuals** **E3b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** **E4b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2 in the same individuals**

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	GMRs and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1a and E2a. If noninferiority of E1a and E2a are both established, E3a and E4a will be assessed sequentially using the same criterion (lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8). The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. Similarly, if noninferiority of E1b and E2b are both established, E3b and E4b will be assessed sequentially using the same criterion (lower bound of the 2-sided 97.5% CI for the difference in percentages is greater than -10%). **GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg** **The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints N1b. **GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** **The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint E1a and E2a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Endpoint	Statistical Analysis Methods
	the primary endpoints E1b and E2b. ***BNT162b2-Naïve Participants:*** **N2a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2** **N2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2** GMR and the associated 2-sided 97.5% CI will be calculated in the same way as for the primary endpoint N1a. Statistical superiority of N2a will be assessed if noninferiority of N1a is established. Superiority of N2a will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 1. The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints N1b. Statistical superiority of N2b will be assessed if noninferiority of N1b is established. Superiority of N2b will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than 0%. **GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2** **The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints N1b.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Endpoint	Statistical Analysis Methods
Secondary immunogenicity (Phase 1)	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
16- to 25-year age group)	2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment. The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2: **GMTs/GMCs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level** GMTs/GMCs and 2-sided 95% CIs will be provided by initial vaccine and age group for the following time points: • At Dose 3 and 7 days and 1 month after Dose 3 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level** GMFRs from before Dose 3 to 7 days and 1 month after Dose 3 and 2-sided 95% CIs will be provided by initial vaccine and age group. GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **GMRs of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2** GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed reference-strain titers for each participant (1 month after Dose 3 – 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. **GMRs of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2** GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (SA-variant titer at 1 month after Dose 3 – reference-strain titer at 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.
Exploratory immunogenicity (Phase 2/3)	**GMTs/GMCs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3:

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	• 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Endpoint	Statistical Analysis Methods
	RCDCs for immunogenicity results Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels after Dose 1 and after Dose 2.
Exploratory immunogenicity (Phase 3, boostability and protection against emerging VOCs)	**GMTs of SARS CoV-2 reference strain neutralizing titers in participants receiving a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$** GMTs and associated 2-sided 95% CIs at Dose 3 and each subsequent time point will be provided for each vaccine group and age group. **GMFRs of SARS CoV-2 reference strain neutralizing titers in participants receiving a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$** GMFRs from Dose 3 to each subsequent time point and associated 2-sided 95% CIs will be provided for each vaccine group and age group. **Geometric mean NT for any VOC not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2** Geometric means and associated 2-sided 95% CIs of any anti-VOC neutralizing titers will be provided at each time point for each group.

9.4.2. Efficacy Analyses

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Endpoint	Statistical Analysis Methods
	in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.
Secondary	**First: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Second: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Endpoint	Statistical Analysis Methods
	Third and fourth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group **Fifth and sixth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints for COVID-19 illness according to CDC-defined symptoms will be evaluated descriptively with 95% CIs. **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days or from 14 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[10] Missing efficacy data will not be imputed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Endpoint	Statistical Analysis Methods
	The following secondary efficacy endpoints regarding asymptomatic SARS-CoV-2 infection will be evaluated based on a success criterion of the lower bound of the 2-sided 95% CI for VE being >20%. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate per 1000 person-years of follow-up in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The hypothesis will be tested if at least 206 cases are accrued. In addition, a descriptive summary of VE against asymptomatic infection over different time intervals (ie, prior to 1 month after Dose 2, from 1 month after Dose 2 onward), along with the associated 2-sided 95% CI, will be calculated using the same method. The analysis of the primary definition of asymptomatic cases will be based on the evaluable efficacy (seroconversion) population and the Dose 2 all-available efficacy population. The analysis of the secondary definition of asymptomatic cases will be based on the Dose 1 all-available efficacy population. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants without evidence of infection (up to the start of asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The hypothesis will be tested if at least 53 cases are accrued. The analysis will be based on the evaluable efficacy (asymptomatic surveillance) population and the all-available efficacy population and will include only participants who are consented to participate in the asymptomatic surveillance and who do not have serological or

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Endpoint	Statistical Analysis Methods
	virological evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period.
Exploratory	**Ratios of confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants without, and with and without, evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** After the primary objectives are met at the final analysis of at least 164 first primary cases, the study will continue with blinded follow-up until the participant is unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. A descriptive update of VE will be provided with additional follow-up data. VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[10] Supportive analysis of time to confirmed COVID-19 illness will be performed using Kaplan-Meier cumulative incidence curves. Participants who were randomized to placebo will be censored at the time of receipt of BNT162b2. **Incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness from 7 days after the second dose will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted. **Incidence of asymptomatic SARS-CoV-2 infection through the entire study follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants who received BNT162b2 and who have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19**

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for asymptomatic infection will be provided for participants who received BNT162b2 at initial randomization and have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with evidence of infection (up to the start of the asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. Participants who are consented to participate in the asymptomatic surveillance and who have serological or virologic evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period will be included in the analysis.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Endpoint	Statistical Analysis Methods
	AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[12] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group. AEs and SAEs reported during the open-label follow-up period will be summarized separately for participants who were unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. For Phase 3 participants enrolled for assessment of boostability and protection against emerging VOCs, descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for local reactions and systemic events from Day 1 through Day 7 after each dose, AEs from Dose 1 to 1 month after the last dose, and SAEs from Dose 1 to 5 or 6 months after the last dose. Local reactions and systemic events from Day 1 through Day 7 after each dose will be presented by severity and cumulatively across severity levels.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Endpoint	Statistical Analysis Methods
	The safety analyses after the first dose and after booster dose(s) are based on the safety population and booster safety population, respectively. Analyses of reactogenicity endpoints are based on a subset of the safety population that includes participants with any e-diary data reported after vaccination. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2: Descriptive statistics will be provided by initial vaccine and age group for local reactions and systemic events from Day 1 through Day 7 after Dose 3, and AEs/SAEs from Dose 3 to 1 month after Dose 3. Local reactions and systemic events from Day 1 through Day 7 after Dose 3 will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs.

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GMFR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing “Process 1” and each lot of “Process 2” will be summarized descriptively. A random sample of 250 participants from those vaccinated

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof in the European Union

with study intervention produced by manufacturing "Process 1" will be selected randomly for the analysis.

Exploratory analyses to investigate possible immunological correlates with efficacy, and characterization of infecting SARS-CoV-2 variants, may be conducted.

The cell-mediated immune response and additional humoral immune response parameters to the reference strain and SA will be summarized for the subset of participants with PBMC samples collected.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Table 6 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8, for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

Only the first primary endpoint will be analyzed at IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints (confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and in all participants, confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection and in all participants) will be evaluated sequentially in the stated order, by the same method used for the evaluation of primary VE endpoints. Success thresholds for secondary VE endpoints will be appropriately chosen to control overall type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Complete safety and immunogenicity analysis approximately 1 month after Dose 3 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

(with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.

- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.

- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.

- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2.

- Safety analyses approximately 1 month after Dose 3 for Phase 3 participants included in the booster evaluation (30 µg or low-dose booster) and approximately 1 month after Dose 2 for newly enrolled Phase 3 participants included in the BNT162b2$_{SA}$ evaluation.

- Immunogenicity analyses approximately 1 month after Dose 3 for Phase 3 participants included in the booster evaluation (30 µg or low-dose booster) and approximately 1 month after Dose 2 for newly enrolled Phase 3 participants included in the BNT162b2$_{SA}$ evaluation, when serology data for the reference strain or for the SA strain are available.

- Analysis of efficacy against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) when a sufficient number of cases have accrued to evaluate the objective(s).

- Complete safety and efficacy analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.

- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met
- Review of safety and/or immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review
- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Up until the final efficacy analysis, 3 blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial. When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
20vPnC	20-valent pneumococcal conjugate vaccine
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCR	B-cell receptor
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
E1, E2, etc	vaccine-experienced (statistical tests)
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Abbreviation	Term
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application in the European Union and any extensions or variations thereof

Abbreviation	Term
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N1, N2, etc	vaccine-naïve (statistical tests)
N/A	not applicable
NAAT	nucleic acid amplification test
NI	noninferiority
non-S	nonspike protein
NT	neutralizing titer
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SA	South Africa
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Abbreviation	Term
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
TCR	T-cell receptor
UK	United Kingdom
ULN	upper limit of normal
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
VOC	variant of concern
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs after accrual of at least 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

10.9. Appendix 9: Genetics

Use/Analysis of DNA and/or RNA

- Genetic variation may impact a participant's response to study intervention, as well as susceptibility to and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA and/or RNA analysis.
- The results of genetic analyses may be reported in a CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA and/or RNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
  - Samples for specified genetic analysis (see Section 8.7) will be stored for up to 15 years or other period as per local requirements.
- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.

4 Centers for Disease Control and Prevention. Emerging SARS-CoV-2 variants. Available from: https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html. Updated: 28 Jan 2021. Accessed: 10 Feb 2021.

5 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

6 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

7 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

8 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

9 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

10 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

11 Agresti A, Min Y. Simple improved confidence intervals for comparing matched proportions. Stat Med 2005;24(5):729-40.

12 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 17 Clean Copy, 20Jul2021
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	20-Jul-2021 12:16:37	Business Line Approver
PPD	20-Jul-2021 12:25:22	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197995fd1\Approved\Approved On: 20-Jul-2021 12:25 (GMT)

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 16	28 May 2021	• Removed the requirement to conduct a potential COVID-19 convalescent visit following each potential COVID-19 illness visit. • Clarified that only non-Pfizer interventional studies for prevention of COVID-19 are prohibited throughout study participation. • Clarified that during the 7 days following each vaccination (either as part of this study, co-enrolled C459 studies, or the B7471026 [20vPnC] study), potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. • Revised the noninferiority margin from 2-fold to 1.5-fold and added a minimum GMR point estimate of ≥0.8 as another success criterion for Phase 3 booster and VOC immunogenicity assessment. Noninferiority is met if the lower limit of the alpha-adjusted CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.8. • Added Phase 1 booster participants to the Dose 3 booster immunogenicity population definitions. • Included a booster safety population definition. • Clarified that the interim analyses for booster immunogenicity will be conducted when serology data for the reference strain or for the SA strain are available.
Protocol amendment 15	25 March 2021	• In order to further characterize booster responses induced by BNT162b2, 2 additional lower-dose booster groups have been added to the subset for evaluation of boostability and protection against emerging VOCs. An additional 5-µg or 10-µg dose of BNT162b2 will be given to approximately 144 Phase 3 participants approximately 5 to 7 months after their second dose of BNT162b2. • To further describe cell-mediated immune responses following isolations of PBMCs in a subset of both the Phase 3 participants who receive a single booster vaccination and the BNT162b2-naïve group who receive BNT162b2$_{SA}$, additional genetic testing may also

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		be performed; corresponding details and an appendix have been added. • An exploratory objective was added for Phase 3 participants to describe the immune response to a third dose of BNT162b2 or a third or fourth dose of BNT162b2$_{SA}$ at later time points to align with analyses and corresponding changes detailed in the statistical section. • Removed the lower age limit for eligibility for administration of BNT162b2 to those originally assigned to placebo: this will now be covered in the recommendations detailed separately, and available in the electronic study reference portal. • Allowed administration of BNT162b2 at Visits 101 and 102 to pregnant participants in certain circumstances. • To align with contraception requirements, reduced the EDP reporting period to 28 days after the last dose of study intervention.

Protocol amendment 14	02 March 2021	• In order to further describe duration of protection, and heterologous/homologous protection against the emerging VOCs, an additional dose of BNT162b2 or BNT162b2$_{SA}$ will be given to approximately 600 Phase 3 participants approximately 5 to 7 months after their second dose of BNT162b2; a further dose of BNT162b2$_{SA}$ will be given to approximately 30 of those participants who receive BNT162b2$_{SA}$:
		  • Added corresponding objectives, estimands, and endpoints
		  • Added corresponding SoA and procedures
		  • Added details in the statistical methods sections.
		• Approximately 300 BNT162b2-naïve participants will be enrolled and receive 2 doses of BNT162b2$_{SA}$ to describe heterologous/homologous protection against the emerging VOCs and reference strains:
		  • Added corresponding objectives, estimands, and endpoints
		  • Added corresponding SoA and procedures
		  • Added details in the statistical methods sections.
		• Cell-mediated immune responses will also be described following isolations of PBMCs in a subset of both the Phase 3 participants who

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		receive a single booster vaccination and the BNT162b2-naïve group who receive $BNT162b2_{SA}$. • Added the asymptomatic case definitions in Section 8.1 and further clarified the secondary definition for asymptomatic case based on seroconversion of N-binding antibody. • Defined the analysis populations used for evaluation of asymptomatic infection based on seroconversion of N-binding antibody and based on NAAT from participants who consent to active surveillance. • Clarified that unblinding for a nonemergency reason should be conducted outside of the IRT system. • Clarified that if multiple visits occur on the same day, all procedures for all visits must be conducted (including collection of all blood samples). • Clarified the plan for stepwise unblinding of the sponsor in the study.

Protocol amendment 13	12 February 2021	• In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2:
		  • Added corresponding objectives, estimands, and endpoints
		  • Added corresponding SoA and procedures
		  • Added details in the statistical methods sections.
		• Clarified the population used for analysis of reactogenicity endpoints.
		• To align with current recommendations, investigators may exercise judgment on review of inclusion and exclusion criteria ahead of vaccination with BNT162b2 for participants who originally received placebo.
		• Clarified that if a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent.
		• Participants who provide biweekly swabs for surveillance of asymptomatic infection should now continue to swab even after unblinding if

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		they originally received BNT162b2, to maximize the numbers of swabs to be collected. • Clarified the procedures for unscheduled visits to administer a second dose in the event a participant received only 1 dose of BNT162b2.
Protocol amendment 12	14 January 2021	• Because of a formatting error in protocol amendment 11, exclusion criterion 4 was inadvertently added to exclusion criterion 3 and the subsequent criteria renumbered. This amendment corrects that error. • Because of a change in the pace with which participants ≥16 years of age who originally received placebo will become eligible for receipt of BNT162b2, text was updated throughout the protocol to reflect that this will happen in a phased manner, with recommendations detailed separately and available in the electronic study reference portal. • Clarified that participants who are unblinded because they become potentially eligible for receipt of BNT162b2 will not participate in surveillance for asymptomatic SARS CoV-2 infection. • Corrected the exploratory objective to describe non-S seroconversion to SARS-CoV-2 to clarify that this will only include participants who received BNT162b2 at initial randomization (since those who received it subsequently do not have blood drawn). • In line with current recommendations, removed the requirement to discontinue study intervention because of a diagnosis of COVID-19 during the study.

Protocol amendment 11	04 January 2021	• Added approaches to evaluate efficacy against asymptomatic SARS-CoV-2 infection:
		  • Added objectives, estimands, and endpoints, and statistical methods, for assessment via N-binding antibody seroconversion;
		  • Added a potential intensive surveillance period for nasal swabbing, for assessment via NAAT:
		  • Corresponding objectives, estimands, and endpoints added
		  • Corresponding SoA and procedures added
		  • Details added in the statistical methods sections.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Added the possibility of assessing full-length S-binding, instead of S1-binding, IgG levels in Phase 2/3. • Clarified in Section 4.1.1 that any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity at the approximate time participants in Phase 2/3 reach Visit 4, for consistency with other sections. • Added a sentence to reflect that assent is obtained from participants <18 years of age.
Protocol amendment 10	01 December 2020	• Added the possibility of administering BNT162b2 to participants who originally received placebo, following any local or national recommendations. • Added the possibility of administering BNT162b2 to participants who originally received placebo, following completion of the active safety surveillance period. • Added corresponding exploratory objectives and statistical analysis details. • Removed immunogenicity analyses of titers greater than defined threshold(s). • Removed the need for blinded COVID-19 case review after the final efficacy analysis. • Included the possibility, due to local circumstances related to the COVID-19 pandemic, that study procedures that do not require in-person participant contact may be performed by telehealth. • In light of additional information to better estimate the standard deviation of SARS-CoV-2 neutralizing titers, increased the sample size for the noninferiority immunogenicity analysis in adolescents 12 to 15 years of age.
Protocol amendment 9	29 October 2020	• To better align with the natural history of SARS-CoV-2 infection, added Phase 2/3 secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days after the second dose; also modified the existing secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days, as well as 7 days, after the second dose; • Made corresponding changes to the study design, study assessments and procedures, and statistical analysis sections. • For operational reasons, removed the interim analysis planned after accrual of 32 cases.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified that interim analyses will be conducted after accrual of *at least* 62, 92, and 120 cases. • Included any participants 16 through 17 years of age enrolled under this amendment in the reactogenicity subset. • Added an unblinded clinical scientist to support DMC activities. • Clarified that serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.
Protocol amendment 8	15 October 2020	• Removed "N-binding antibody" and "SARS-CoV-2 detection by NAAT" as endpoints from the third exploratory objective, as these results are used for the determination of the population, and are not endpoints. • Clarified that the "Process 1" participants included in the descriptive analysis of "Process 1"- and "Process 2"-manufactured study interventions will be selected randomly. • Clarified that surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study. • Further modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Clarified that for participants who are not in the reactogenicity subset, local reactions and systemic events following vaccination should be detected and reported as AEs. • Clarified that premenarchal females are not WOCBP. • Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2. • Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2."

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified the degree of unblinding on the unblinded submissions team in Section 6.3.3. • Made provision for a second dose of BNT162b2 in participants who were affected by a medication error at Visit 2 in Section 6.6. • Provided further clarification regarding discontinuation of study intervention in Section 7.1. • Modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Added that 2 periods of potential COVID-19 symptoms within 4 days will be considered as a single illness. • Provided guidance in Section 8.13 regarding circumstances in which a SARS-CoV-2 test might be required even if symptoms within 7 days following each vaccination are considered more likely due to vaccine reactogenicity. • Made allowance in Section 8.13 for a second SARS-CoV-2 test to be performed within the same potential COVID-19 illness if it is in accordance with routine practice. • Added Section 8.15 to describe the reporting of SARS-CoV-2 test results and their implications for participants receiving a second vaccine dose. • Added statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age. • Amended scope of analyses of safety data in Section 9.5.1. • Made various editorial changes.
Protocol amendment 6 (Germany-specific)	23 September 2020	• According to regulatory request, inclusion criterion 1 now specifies that participants less than 18 years of age will not be enrolled in the EU.
Protocol amendment 6	08 September 2020	• Reordered some procedures in the Phase 2/3 schedule of activities for consistency with the main body of the protocol. • Corrected the window for the 6-month follow-up visit to be approximately 6 months after Vaccination 2. • Reduced the volume of blood draws to ~20 mL. • Removed the need to have safety data reported for participants to be included in the safety objective assessment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease. • Increased the sample size for Phase 2/3 to ~43,998. • Clarified that inclusion criterion 4 (ie, participants at higher risk for acquiring COVID-19) is applicable for Phase 2/3 only, and provided some examples. • Removed exclusion criterion 2 (ie, known infection with HIV, HCV, or HBV) for Phase 3 and added criteria for HIV-positive participants. • Decreased the lower age limit and removed the upper age limit for inclusion in Phase 2/3 in order to evaluate BNT162b2 30 µg in older adolescents and those over 85 years of age; updated the title and other references to adults to align with this change. • Renamed the immunological assays to align with other program-level documents. • Removed reference to the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) being "heads up." • Clarified that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention. • Added clarification that potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. • Updated the analysis population descriptions to align with the study SAP.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory. • Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7. • Updated the stopping and alert rule parameters for enhanced COVID-19.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 23
LIST OF FIGURES 23
1. PROTOCOL SUMMARY 24
1.1. Synopsis 24
1.2. Schema 38
1.3. Schedule of Activities 39
1.3.1. Phase 1 39
1.3.2. Phase 2/3 46
1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo 50
1.3.4. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) 52
1.3.5. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants 55
1.3.6. Surveillance for Asymptomatic SARS-CoV-2 Infection 58
2. INTRODUCTION 59
2.1. Study Rationale 59
2.2. Background 59
2.2.1. Clinical Overview 61
2.3. Benefit/Risk Assessment 61
2.3.1. Risk Assessment 63
2.3.2. Benefit Assessment 65
2.3.3. Overall Benefit/Risk Conclusion 65
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 65
3.1. For Phase 1 65
3.2. For Phase 2/3 67
4. STUDY DESIGN 74
4.1. Overall Design 74
4.1.1. Phase 1 75
4.1.2. Phase 2/3 76
4.2. Scientific Rationale for Study Design 79
4.3. Justification for Dose 79

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

4.4. End of Study Definition 80
5. STUDY POPULATION 81
5.1. Inclusion Criteria 81
5.2. Exclusion Criteria 82
5.3. Lifestyle Considerations 85
5.3.1. Contraception 85
5.4. Screen Failures 85
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 85
6. STUDY INTERVENTION 86
6.1. Study Intervention(s) Administered 87
6.1.1. Manufacturing Process 87
6.1.2. Administration 88
6.2. Preparation/Handling/Storage/Accountability 88
6.2.1. Preparation and Dispensing 89
6.3. Measures to Minimize Bias: Randomization and Blinding 90
6.3.1. Allocation to Study Intervention 90
6.3.2. Blinding of Site Personnel 90
6.3.3. Blinding of the Sponsor 91
6.3.4. Breaking the Blind 92
6.4. Study Intervention Compliance 92
6.5. Concomitant Therapy 93
6.5.1. Prohibited During the Study 93
6.5.2. Permitted During the Study 94
6.6. Dose Modification 94
6.7. Intervention After the End of the Study 95
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 95
7.1. Discontinuation of Study Intervention 95
7.2. Participant Discontinuation/Withdrawal From the Study 96
7.2.1. Withdrawal of Consent 97
7.3. Lost to Follow-up 97

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8. STUDY ASSESSMENTS AND PROCEDURES 97
8.1. Efficacy and/or Immunogenicity Assessments 99
8.1.1. Efficacy Against COVID-19 99
8.1.2. Efficacy Against Asymptomatic SARS-CoV-2 Infection 101
8.1.2.1. Seroconversion of N-Binding Antibody 101
8.1.2.2. NAAT-Confirmed SARS-CoV-2 Infection 101
8.1.3. Vaccine-Induced Immunogenicity 102
8.1.4. Biological Samples 102
8.1.5. Surveillance for Asymptomatic SARS-CoV-2 Infection 103
8.2. Safety Assessments 103
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 103
8.2.2. Electronic Diary 104
8.2.2.1. Grading Scales 105
8.2.2.2. Local Reactions 105
8.2.2.3. Systemic Events 106
8.2.2.4. Fever 107
8.2.2.5. Antipyretic Medication 108
8.2.3. Phase 1 Stopping Rules 108
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 109
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 110
8.2.6. Pregnancy Testing 110
8.3. Adverse Events and Serious Adverse Events 110
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 111
8.3.1.1. Reporting SAEs to Pfizer Safety 112
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 112
8.3.2. Method of Detecting AEs and SAEs 112
8.3.3. Follow-up of AEs and SAEs 113
8.3.4. Regulatory Reporting Requirements for SAEs 113
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 113
8.3.5.1. Exposure During Pregnancy 113

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

8.3.6. Exposure During Breastfeeding 115
8.3.6.1. Occupational Exposure 115
8.3.7. Cardiovascular and Death Events 116
8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 116
8.3.9. Adverse Events of Special Interest 116
8.3.9.1. Lack of Efficacy 116
8.3.10. Medical Device Deficiencies 117
8.3.11. Medication Errors 117
8.4. Treatment of Overdose 118
8.5. Pharmacokinetics 118
8.6. Pharmacodynamics 118
8.7. Genetics 118
8.8. Biomarkers 118
8.9. Immunogenicity Assessments 119
8.10. Health Economics 119
8.11. Study Procedures 119
8.11.1. Phase 1 119
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 119
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 120
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 123
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 124
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 125
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 127
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 129
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 130
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4) 130
8.11.1.10. Between Visits 8 and 9 131

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2) 131
8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a)....133
8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a)....133
8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2....134
8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2....135
8.11.2. Phase 2/3....135
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 135
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 138
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)....140
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)....141
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 141
8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 142
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 143
8.13. COVID-19 Surveillance (All Participants) 144
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 145
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)....146
8.14. Communication and Use of Technology....146
8.15. SARS-CoV-2 NAAT Results....147

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo 148
8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2) 148
8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101) 149
8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102) 150
8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102) 151
8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102) 152
8.17. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) 152
8.17.1. Visit 301 – Vaccination 3: (150 to 210 Days After Visit 2) 152
8.17.2. Visit 302 – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 301) 154
8.17.3. Visit 303 – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 301) 155
8.17.4. Visit 304 – 1-Week Follow-up Visit (Vaccination 4): (6 to 8 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$ 157
8.17.5. Visit 305 – 1-Month Follow-up Visit (Vaccination 4): (28 to 35 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$ 157
8.17.6. Visit 306 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 301): 158
8.17.7. Visit 307 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 301): 159
8.18. Administration of BNT162b2$_{SA}$ to BNT162b2-naïve Participants 159
8.18.1. Visit 401 – Vaccination 1: (Day 1) 159
8.18.2. Visit 402 – Vaccination 2: (19 to 23 Days After Visit 401) 162
8.18.3. Visit 403 – 1-Week Follow-up Visit (After Vaccination 2): (6 to 8 Days After Visit 402) 163
8.18.4. Visit 404 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 402) 164
8.18.5. Visit 405 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 402) 165

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.18.6. Visit 406 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 402) 166
8.19. Surveillance for Asymptomatic SARS-CoV-2 Infection 166
8.19.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11 166
8.19.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection 167
9. STATISTICAL CONSIDERATIONS 168
9.1. Estimands and Statistical Hypotheses 168
9.1.1. Estimands 168
9.1.2. Statistical Hypotheses 169
9.1.2.1. Statistical Hypothesis Evaluation for Efficacy 169
9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity 169
9.2. Sample Size Determination 171
9.2.1. Phase 1 171
9.2.2. Efficacy Against COVID-19 171
9.2.3. Efficacy Against Asymptomatic Infection 172
9.2.4. Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years 172
9.2.5. Boostability and Protection Against Emerging SARS-CoV-2 VOCs 172
9.2.6. Safety 174
9.3. Analysis Sets 175
9.4. Statistical Analyses 177
9.4.1. Immunogenicity Analyses 177
9.4.2. Efficacy Analyses 187
9.4.3. Safety Analyses 192
9.4.4. Other Analyses 194
9.5. Interim Analyses 195
9.5.1. Analysis Timing 197
9.6. Data Monitoring Committee or Other Independent Oversight Committee 198
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 201
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 201

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

10.1.1. Regulatory and Ethical Considerations 201
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 201
10.1.2. Informed Consent Process 202
10.1.3. Data Protection 203
10.1.4. Dissemination of Clinical Study Data 203
10.1.5. Data Quality Assurance 204
10.1.6. Source Documents 206
10.1.7. Study and Site Start and Closure 206
10.1.8. Sponsor's Qualified Medical Personnel 207
10.2. Appendix 2: Clinical Laboratory Tests 208
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 210
10.3.1. Definition of AE 210
10.3.2. Definition of SAE 211
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 213
10.3.4. Reporting of SAEs 216
10.4. Appendix 4: Contraceptive Guidance 217
10.4.1. Male Participant Reproductive Inclusion Criteria 217
10.4.2. Female Participant Reproductive Inclusion Criteria 217
10.4.3. Woman of Childbearing Potential 218
10.4.4. Contraception Methods 219
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 221
10.6. Appendix 6: Abbreviations 223
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 227
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection 230
10.9. Appendix 9: Genetics 231
11. REFERENCES 232

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

LIST OF TABLES

Table 1. Local Reaction Grading Scale 106
Table 2. Systemic Event Grading Scale 106
Table 3. Scale for Fever 107
Table 4. Power Analysis for Noninferiority Assessment 172
Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 174
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility 196
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses 196
Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall 197
Table 9. Laboratory Abnormality Grading Scale 208
Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 228
Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 229

LIST OF FIGURES

Figure 1. Multiplicity Schema 171

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 3 antigens:

BNT162b1 (variant RBP020.3): a modRNA encoding the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5);

BNT162b2 (variant RBP020.2): a modRNA encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9);

BNT162b2s01 (variant RBP020.11): a modRNA encoding the P2 S containing South Africa B.1.351 variant-specific mutations, hereafter referred to as BNT162b2$_{SA}$, as a representative variant of concern (VOC).

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and/or efficacy of these prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	• GMCs/GMTs at the time of Dose 3 and 7 days and 1 month after Dose 3. • GMFRs from before Dose 3 to 7 days and 1 month after Dose 3 • GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2 • GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
To describe the safety and tolerability profile of BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants, or as 2 doses to BNT162b2-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2-experienced participants	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 5 or 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary Immunogenicity ***BNT162b2-experienced participants***		
To demonstrate the noninferiority of the anti–reference strain immune response after a third dose of BNT162b2 at 30 µg compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate the noninferiority of the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Objectives[a]	Estimands	Endpoints
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
BNT162b2-experienced participants		
To demonstrate the noninferiority of the anti-SA immune response after a third dose of BNT162b2 at 30 µg compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti–reference strain immune response after 1 dose of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ and a third dose of BNT162b2 at 30 µg	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg	SARS-CoV-2 SA NT in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$ or the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Objectives[a]	Estimands	Endpoints
To descriptively compare the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ and the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate a statistically greater anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 SA NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
To descriptively compare the anti–reference strain immune response after 2 doses of BNT162b2$_{SA}$ and after 2 doses of BNT162b2	GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization	In participants who received BNT162b2 at initial randomization: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate and characterize the SARS-CoV-2 isolate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers • Identification of SARS-CoV-2 variant(s)
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers
To describe the immune response to any VOCs not already specified	Geometric mean NT for any VOCs not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2	• SARS-CoV-2 NTs for any VOCs not already specified
To describe the immune response to a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$	• GMTs at Dose 3 and subsequent time points • GMFRs from Dose 3 to subsequent time points	• SARS-CoV-2 reference strain NTs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and SA in a subset of participants: • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 2 doses to BNT162b2-naïve participants • 7 Days and 1 and 6 months after BNT162b2 given as a third dose to BNT162b2-experienced participants		

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for a description of the manufacturing process.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype $BNT162b2_{VOC}$ at 30 µg (based upon the South African variant and hereafter referred to as $BNT162b2_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive $BNT162b2_{SA}$ given as a 2-dose series, separated by 21 days.

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof are europaeu

For evaluation of boostability and protection against emerging VOCs, 600 existing Phase 3 participants 18 to 55 years of age will be rerandomized in a 1:1 ratio to receive either a third dose of BNT162b2 at 30 µg or a third dose of BNT162b2$_{SA}$.

An additional group of 30 existing Phase 3 participants 18 to 55 years of age will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$. For these 30 participants, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the investigator and sponsor will not be. Serum samples from these participants may be used for assay development purposes and, except for objectives relating to response to a fourth dose, their results will be analyzed separately from the main immunogenicity analyses.

A further group of approximately 144 existing Phase 3 participants 18 years of age and older will be enrolled to receive a third, lower, dose of BNT162b2 of either 5 or 10 µg. Approximately 24 participants 18 to 55 years of age and 48 participants >55 years of age will be enrolled in each dose group.

Three hundred participants 18 to 55 years of age who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19 will be enrolled as a new cohort of participants to receive BNT162b2$_{SA}$ given as a 2-dose series.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 5 µg, 10 µg, 20 µg, 30 µg
- BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S containing South Africa B.1.351 variant–specific mutations): 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated. VE will be demonstrated if the lower bound of the 95% CI for VE is >20%.

In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

The boostability and protection against emerging VOCs for BNT162b2-experienced participants and BNT162b2-naïve participants will be assessed based on GMRs of SARS-CoV-2 SA-neutralizing and/or reference strain–neutralizing titers using a 1.5-fold noninferiority margin and the difference in percentages of participants with seroresponse using a 10% noninferiority margin.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

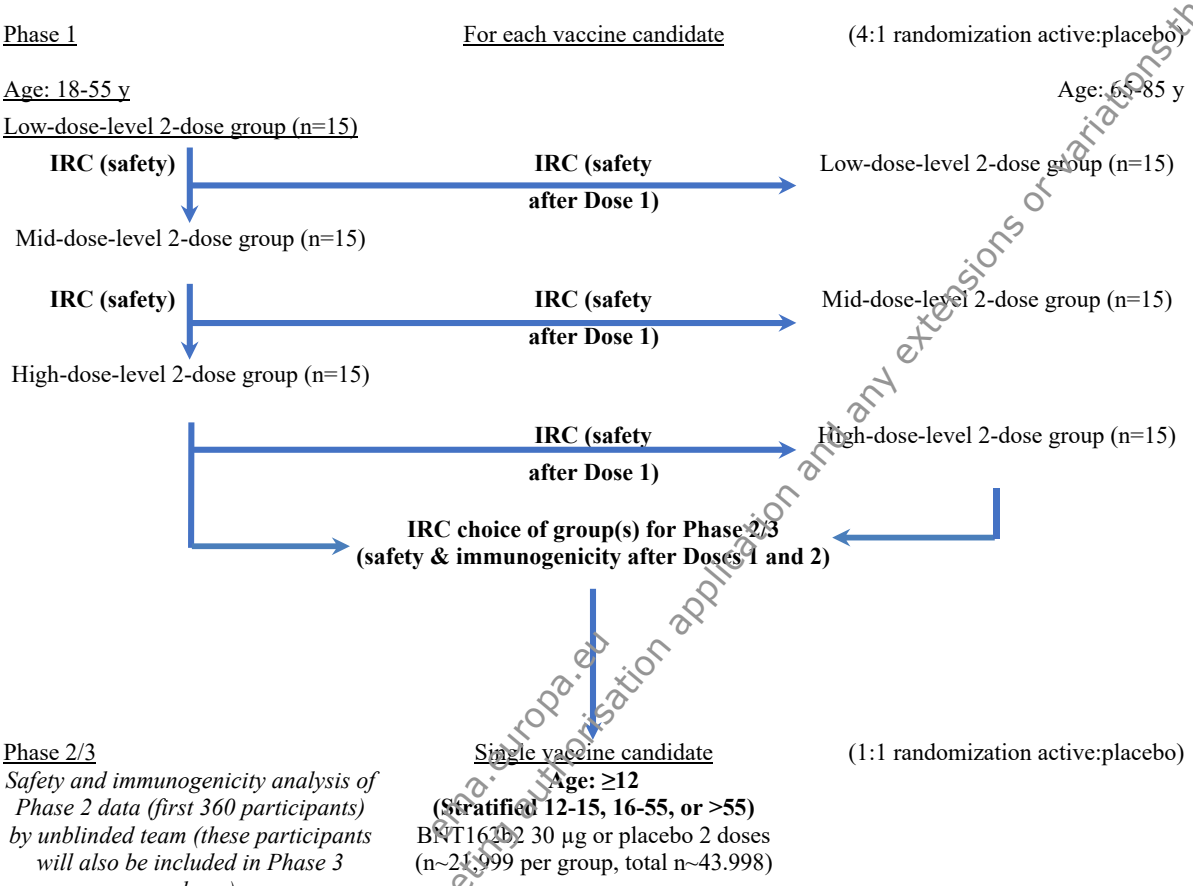
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

Except for the objectives to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age and evaluation of boostability and protection against emerging VOCs by BNT162b2 and BNT162b2$_{SA}$ in Phase 3, the other immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMR, and the associated 95% CIs, for SARS-CoV-2 neutralizing titers, full-length S-binding or S1-binding IgG levels, and/or RBD-binding IgG levels (Phase 1 only) at the various time points.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

1.2. Schema



Abbreviation: IRC = internal review committee.

Note: Participants who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

1.3. Schedule of Activities

The SoA tables provide an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit is required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected. Prior to protocol amendment 16, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b1 or BNT162b2 (at any dose level) will continue in the study as originally planned.

All other participants will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study no later than at the approximate time participants in Phase 2/3 reach Visit 4. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits.

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain informed consent	X								*Continued on table below*	
Assign participant number	X									
Obtain demography and medical history data	X									
Obtain details of medications currently taken	X									
Perform physical examination	X	X	X	X	X	X	X			
Measure vital signs (including body temperature)	X	X	X	X	X	X	X			
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL				
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL									
Serological test for prior COVID-19 infection	~20 mL									
Perform urine pregnancy test (if appropriate)	X	X			X					
Obtain nasal (midturbinate) swab(s)[c]		X			X					X
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X		
Confirm eligibility	X	X			X					
Collect prohibited medication use			X	X	X	X	X	X		X

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Review hematology and chemistry results		X		X	X	X	X		*Continued on table below*	
Review temporary delay criteria		X			X					
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X		
Obtain randomization number and study intervention allocation		X								
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL		
Administer study intervention		X			X					
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X								
Provide thermometer and measuring device		X			X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►	◄	———	►			

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

Visit Number	Screening	1	2	3	4	5	6	7		Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	***Study procedures for Visit 8 onwards continue on the next table***	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X		*Continued on table below*	
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X		X
Collect e-diary or assist the participant to delete application										
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)										X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**		
Obtain informed consent		X					
Confirm participant originally received 10 to 30 µg of BNT162b1 or BNT162b2		X					
Perform urine pregnancy test (if appropriate)		X					
Confirm use of contraceptives (if appropriate)		X	X	X			
Collect prohibited medication use	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X			
Measure body temperature		X					
Confirm eligibility		X					
Review temporary delay criteria		X					
Collect blood sample for immunogenicity assessment	~20 mL	~20 mL	~20 mL	~20 mL	~20 mL	~20 mL	
Obtain nasal (midturbinate) swab(s)		X					X

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**		
Obtain the participant's vaccine vial allocation using the IRT system		X					
Administer 30-µg dose of BNT162b2		X					
Assess acute reactions for at least 30 minutes after study intervention administration		X					
Provide thermometer and measuring device		X					
Remind participant of e-diary technologies		X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		←	→				

090177e19727636\8\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and its extensions or variations thereof
ema.europa.eu

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**		
Review ongoing reactogenicity e-diary symptoms and obtain stop dates				X			
Collect AEs and SAEs as appropriate	X	X	X	X	X[b]	X[b]	X
Collect e-diary or assist the participant to delete application						X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: IRT = interactive response technology; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit is required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C. Prior to protocol amendment 16, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b2 or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b2 will continue in the study as originally planned.

All other participants who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4). If they want to receive BNT162b2, they will be unblinded and those who did originally receive placebo will move to the SoA in Section 1.3.3 for their remaining visits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Obtain informed consent	X						
Assign participant number	X						
Obtain demography and medical history data	X						
Perform clinical assessment[c]	X						
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X	
Measure height and weight	X						
Measure temperature (body)	X	X					
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X	X				
Collect nonstudy vaccine information	X	X	X	X			
Collect prohibited medication use		X	X	X	X	X	X
Confirm eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	
Obtain nasal (midturbinate) swab	X	X					X
Obtain randomization number and study intervention allocation	X						
Administer study intervention	X	X					

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X						
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	←	←					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X				
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X
According to eligibility, ascertain willingness to receive BNT162b2 if originally received placebo; if willing, unblind the participant's study intervention assignment (if not already done), and move placebo recipients to the SoA in Section 1.3.3			X	← X			
Collect e-diary or assist the participant to delete application						X	

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. Any placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2.

Visit Number	101	102	103	104	105	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**105 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Confirm participant meets local/national recommending criteria or is at least 175 days after Vaccination 2 (Visit 4/Visit 2)	X					
Obtain informed consent	X					
Confirm participant originally received placebo	X					
Perform urine pregnancy test (if appropriate)	X	X				
Confirm use of contraceptives (if appropriate)	X	X				
Collect prohibited medication use	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	
Review and consider eligibility	X	X				
Review temporary delay criteria	X	X				
Collect blood sample for immunogenicity assessment[c]	~20 mL					
Obtain nasal (midturbinate) swab	X	X				X
Obtain vaccine vial allocation via IRT	X	X				
Administer BNT162b2	X	X				
Assess acute reactions for at least 30 minutes after study intervention administration	X	X				

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu

Visit Number	101	102	103	104	105	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Collect AEs and SAEs as appropriate	X	X	X	X		X[d]
Contact the participant by telephone			X	X	X	
Request the participant return the e-diary or assist the participant to delete the application					X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)						X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

a. For participants who become eligible according to recommendations detailed separately and available in the electronic study reference portal.
b. For any remaining Phase 2/3 placebo recipients who wish to receive BNT162b2; may be combined with Visit 4 for Phase 2/3 participants.
c. Only if the participant has no blood sample collected in the previous 7 days.
d. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.4. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg)

Select participants in Phase 3 at select sites who originally received 2 doses of BNT162b2 will be offered the opportunity to receive a third (and potentially fourth) dose of BNT162b2 or BNT162b2$_{SA}$.

Visit Number	301	302	303	304	305	306	307	Unplanned
Visit Description	Vax 3[a]	1-Week Follow-up Visit (After Vax 3)	1-Month Follow-up Visit (After Vax 3)	1-Week Follow-up Visit (After Vax 4)[b]	1-Month Follow-up Visit (After Vax 4)[b]	6-Month Follow-up Visit	18-Month Follow-up Visit	Potential COVID-19 Illness Visit[c]
Visit Window (Days)	150 to 210 Days After Visit 2	6 to 8 Days After Visit 301	28 to 35 Days After Visit 301	6 to 8 Days After Visit 303	28 to 35 Days After Visit 303	175 to 189 Days After Visit 301	532 to 560 Days After Visit 301	Optimally Within 3 Days After Potential COVID-19 Illness Onset
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4				
Obtain informed consent	X							
Confirm participant originally received BNT162b2 at Dose 1 and Dose 2	X							
Perform urine pregnancy test (if appropriate)	X		X[b]					
Confirm use of contraceptives (if appropriate)	X	X	X	X	X			
Collect prohibited medication use	X	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X	X	X		
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X			X	X	
Measure body temperature	X		X[b]					
Confirm eligibility	X		X[b]					
Review temporary delay criteria	X		X[b]					

This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Visit Number	301	302	303	304	305	306	307	Unplanned
Visit Description	**Vax 3[a]**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**1-Week Follow-up Visit (After Vax 4)[b]**	**1-Month Follow-up Visit (After Vax 4)[b]**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**150 to 210 Days After Visit 2**	**6 to 8 Days After Visit 301**	**28 to 35 Days After Visit 301**	**6 to 8 Days After Visit 303**	**28 to 35 Days After Visit 303**	**175 to 189 Days After Visit 301**	**532 to 560 Days After Visit 301**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			**ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4**				
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation[d]	~120 mL	~120 mL	~120 mL			~120 mL		
Collect blood sample for HLA typing[d]	~5 mL							
Obtain nasal (midturbinate) swab(s)	X		X[b]					X
Obtain randomization number and study intervention allocation using the IRT system	X							
Administer study intervention	X		X[b]					
Assess acute reactions for at least 30 minutes after study intervention administration	X		X[b]					
Provide thermometer and measuring device	X							
Remind participant of e-diary technologies	X		X[b]					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	←	→		↔				

090177e19727636\8Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	301	302	303	304	305	306	307	Unplanned
Visit Description	Vax 3[a]	1-Week Follow-up Visit (After Vax 3)	1-Month Follow-up Visit (After Vax 3)	1-Week Follow-up Visit (After Vax 4)[b]	1-Month Follow-up Visit (After Vax 4)[b]	6-Month Follow-up Visit	18-Month Follow-up Visit	Potential COVID-19 Illness Visit[c]
Visit Window (Days)	150 to 210 Days After Visit 2	6 to 8 Days After Visit 301	28 to 35 Days After Visit 301	6 to 8 Days After Visit 303	28 to 35 Days After Visit 303	175 to 189 Days After Visit 301	532 to 560 Days After Visit 301	Optimally Within 3 Days After Potential COVID-19 Illness Onset
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4				
Review ongoing reactogenicity e-diary symptoms and obtain stop dates			X		X			
Collect AEs and SAEs as appropriate	X	X	X	X	X	X[e]	X[e]	X
Collect e-diary or assist the participant to delete application							X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)								X

Abbreviations: e-diary = electronic diary; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; vax = vaccination.

a. Visit 301 can occur on the same day as Visit 4, but all procedures for both visits must be conducted (including collection of all blood samples).
b. Only for those participants who will receive Dose 4.
c. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
d. Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants who will receive a third (but not fourth) dose of BNT162b2 at 30 µg or $BNT162b2_{SA}$ at select sites only.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

1.3.5. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants

As part of Amendment 14, an additional cohort of BNT162b2-naïve participants will be enrolled to receive BNT162b2$_{SA}$ per the following SoA.

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain informed consent	X						
Assign participant number	X						
Obtain demography and medical history data	X						
Perform clinical assessment[c]	X						
Measure height and weight	X						
Measure temperature (body)	X	X					
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X	X	X			
Collect nonstudy vaccine information	X	X	X	X	X		
Collect prohibited medication use		X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X			X	X	X	
Confirm eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment	~50 mL		~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation[d]	~120 mL		~120 mL	~120 mL	~120 mL		
Collect blood sample for HLA typing[d]	~5 mL						

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain nasal (midturbinate) swab	X	X					X
Obtain the participant's vaccine vial allocation using the IRT system	X	X					
Administer BNT162b2$_{SA}$	X	X					
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X						
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	◄►	◄►					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X		X			
Collect AEs and SAEs as appropriate	X	X	X	X	X[e]	X[e]	X
Collect e-diary or assist the participant to delete application						X	

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: e-diary = electronic diary; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; vax = vaccination.

a. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
b. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
c. Including, if indicated, a physical examination.
d. Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants at select sites only.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

1.3.6. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4 or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

Visit Number	201	202 Onward
Visit Description	**Asymptomatic SARS-CoV-2 Infection Surveillance Consent**	**Asymptomatic SARS-CoV-2 Infection Surveillance Swab**
Visit Window (Days)	**From Approval of Protocol Amendment 11**	**Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection**
Obtain informed consent for asymptomatic SARS-CoV-2 infection surveillance	X	
Collect prohibited medication use	X	
Collect blood sample for immunogenicity assessment[a]	~20 mL/~10 mL	
Obtain nasal (midturbinate) swab (self-swab at home or by site staff at an in-person visit)	X	X
Collect AEs and SAEs as appropriate[b]	X	

a. Only if the participant has no blood sample collected in the previous 7 days. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
b. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no licensed vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

As more data about COVID-19 continue to accrue, the potential duration of protection afforded after a wild-type SARS-CoV-2 infection, and by vaccination, remains unknown. In addition, mutated SARS-CoV-2 VOCs have started to emerge, for example in the UK (known as 20I/501Y.V1, VOC 202012/01, or B.1.1.7), SA (known as 20H/501Y.V2 or B.1.351), and Brazil (known as P.1).[4]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[5,6]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may

be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Three SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 3 antigens:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5);

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9);

- **BNT162b2s01** (variant RBP020.11): nucleoside-modified messenger RNA (modRNA) as above, but encoding the P2 S containing South Africa B.1.351 variant–specific mutations, hereafter referred to as BNT162b2$_{SA}$, as a representative variant of concern (VOC).

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

In light of the unknowns regarding duration of protection, as well as the emerging VOCs, it is important to understand the boostability of BNT162, and potential heterologous protection against emerging VOC(s). A first step to address this will be to study an additional dose of BNT162b2 at 30 µg given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ (based upon the South African variant and hereafter referred to as BNT162b2$_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

This document can only be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[7] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[8] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with the currently available therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.

- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.

- All participants 12 to 15 years of age will be included in the reactogenicity subset (see Section 8.2.2).

This document cannot be used to support a marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[9]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of an efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	• GMCs/GMTs at the time of Dose 3 and 7 days and 1 month after Dose 3. • GMFRs from before Dose 3 to 7 days and 1 month after Dose 3	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels
	• GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers
	• GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives	Estimands	Endpoints
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Objectives[a]	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants, or as 2 doses to BNT162b2-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2-experienced participants	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 5 or 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary Immunogenicity ***BNT162b2-experienced participants***		
To demonstrate the noninferiority of the anti–reference strain immune response after a third dose of BNT162b2 at 30 µg compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
BNT162b2-naïve participants		
To demonstrate the noninferiority of the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
BNT162b2-experienced participants		
To demonstrate the noninferiority of the anti-SA immune response after a third dose of BNT162b2 at 30 µg compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Objectives[a]	Estimands	Endpoints
To demonstrate the noninferiority of the anti–reference strain immune response after 1 dose of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ and a third dose of BNT162b2 at 30 µg	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg	SARS-CoV-2 SA NT in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$ or the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ and the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate a statistically greater anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 SA NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
To descriptively compare the anti–reference strain immune response after 2 doses of BNT162b2$_{SA}$ and after 2 doses of BNT162b2	GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Objectives[a]	Estimands	Endpoints
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization	In participants who received BNT162b2 at initial randomization: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate and characterize the SARS-CoV-2 isolate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers • Identification of SARS-CoV-2 variant(s)
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers
To describe the immune response to any VOCs not already specified	Geometric mean NT for any VOCs not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2	• SARS-CoV-2 NTs for any VOCs not already specified
To describe the immune response to a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$	• GMTs at Dose 3 and subsequent time points • GMFRs from Dose 3 to subsequent time points	• SARS-CoV-2 reference strain NTs
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and SA in a subset of participants: • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 2 doses to BNT162b2-naïve participants • 7 Days and 1 and 6 months after BNT162b2 given as a third dose to BNT162b2-experienced participants		

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for description of the manufacturing process.

Up until the final efficacy analysis, this protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ at 30 µg (based upon the South African variant and hereafter referred to as

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

BNT162b2$_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than at the approximate time participants in Phase 2/3 reach Visit 4.

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162.

Participants are expected to participate for up to a maximum of approximately 26 months.

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 280 participants from each of the 2 age groups (12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

For evaluation of boostability and protection against emerging VOCs, 600 existing Phase 3 participants 18 to 55 years of age will be rerandomized in a 1:1 ratio to receive either a third dose of BNT162b2 at 30 µg or a third dose of BNT162b2$_{SA}$.

A further group of approximately 144 existing Phase 3 participants 18 years of age and older will be enrolled to receive a third, lower, dose of BNT162b2 of either 5 or 10 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Approximately 24 participants 18 to 55 years of age and 48 participants >55 years of age will be enrolled in each dose group. An additional group of 30 existing Phase 3 participants 18 to 55 years of age will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$. For these 30 participants, through 1 month after their first dose of BNT162b2$_{SA}$ the participant will be blinded to their vaccine allocation but the investigator and Sponsor will not be. Serum samples from these participants may be used for assay development purposes and, except for objectives relating to response to a fourth dose, their results will be analyzed separately from the main immunogenicity analyses.

Three hundred participants 18 to 55 years of age who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19 will be enrolled as a new cohort of participants to receive BNT162b2$_{SA}$ given as a 2-dose series.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 2/3 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4).

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

The changes to the protocol as part of protocol amendment 14 to assess boostability and homologous/heterologous protection against emerging VOCs allow the evaluation of safety and immunogenicity of BNT162b2$_{SA}$:

- When given as a third dose to C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously (ie, BNT162b2-experienced) and have not experienced COVID-19.
- In a small separate group of individuals who previously received 2 doses of BNT162b2 followed by 1 dose of BNT162b2$_{SA}$, a second BNT162b2$_{SA}$ dose will also be given 1 month after Dose 1 of BNT162b2$_{SA}$.
- When given as a 2-dose series, separated by 21 days, in newly recruited participants who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

In addition, a group of C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously will receive a third dose of BNT162b2.

This approach will allow an evaluation of immunogenicity against the reference ancestral SARS-CoV-2 strain (Wuhan-Hu-1/USA-WA1) and the selected South African VOC using a noninferiority approach based on neutralizing antibody titers in prior BNT162b2 vaccinees who receive either a homologous boost (with BNT162b2) or a heterologous boost (with BNT162b2$_{SA}$), as well as new vaccinees receiving 2 doses of BNT162b2$_{SA}$.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.6. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness visit will occur and, prior to protocol amendment 16, a subsequent convalescent visit would occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization.

   For the boostability and protection-against-VOCs subset:

   - Existing participants enrolled to receive a third dose of BNT162b2 at 30 µg or BNT162b2$_{SA}$; male or female participants between the ages of 18 and 55 years, inclusive, at rerandomization.
   - Newly enrolled participants enrolled to receive 2 doses of BNT162b2$_{SA}$; male or female participants between the ages of 18 and 55 years, inclusive, at enrollment.
   - Existing participants enrolled to receive a third dose of BNT162b2 at 5 or 10 µg; male or female participants ≥18 years at rerandomization.

   Note that participants <18 years of age cannot be enrolled in the EU.

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during

the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

5. **Boostability and protection-against-VOCs existing participant subset only:** Participants who provided a serum sample at Visit 3, with Visit 3 occurring within the protocol-specified window.

Informed Consent:

6. Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Chronic pulmonary disease
- Asthma
- Current vaping or smoking
- History of chronic smoking within the prior year
- Chronic liver disease
- Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
- Resident in a long-term facility
- BMI >30 kg/m^2
- Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e19727636\8\Approved\Approved On: 28-May-2021 17:50 (GMT)

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry through and including 6 months after the last dose of study intervention, with the exception of non-Pfizer interventional studies for prevention of COVID-19, which are prohibited throughout study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Sore throat;
- Diarrhea;
- Vomiting.

2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.

3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 3 investigational RNA vaccine candidates, with the addition of saline placebo, are the 4 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 5 µg, 10 µg, 20 µg, 30 µg
- BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S containing South Africa B.1.351 variant–specific mutations): 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof in the European Union.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	5-, 10-, 20-, 30-µg	30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. Participants who originally received placebo and accept the offer to receive BNT162b2 at defined points as part of the study will receive 1 dose of BNT162b2 at each additional vaccination visit (Visits 101 and 102) in accordance with the study's additional SoA (Section 1.3.3). The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162 at Visit 8a.

Participants in the subset for evaluation of boostability and protection against emerging VOCs will receive either a third dose of BNT162b2 or BNT162b2$_{SA}$ approximately 5 to 7 months after their second dose of BNT162 at Visit 301. Of those who receive BNT162b2$_{SA}$ at Visit 301, a subset will receive a further dose of BNT162b2$_{SA}$ at Visit 303.

BNT162b2-naïve participants who are enrolled under protocol amendment 14 to receive BNT162b2$_{SA}$ will receive 1 dose of study intervention at each vaccination visit, Visits 401 and 402.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

9. Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

To allow administration of BNT162b2 to participants who originally received placebo, site staff will be unblinded to individual participants' original study intervention allocation as the participants become eligible for vaccination under local/national recommendations or from 6 months after the second dose.

For the group of 30 existing Phase 3 participants 18 to 55 years of age who will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the investigator will not be.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).

- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.

- An unblinded team supporting interactions with and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

- After the formal data release of the final efficacy analysis of at least 164 cases, which is considered the primary completion of the study efficacy objectives, additional statisticians and programmers will become unblinded at the participant level to prepare unblinded analyses and other regulatory activities. A group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study.

- After the study data used for submission become public, the blinded study team will also have access to those data, and become unblinded at a group level.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- When a participant is unblinded for potential receipt of BNT162b2 (if he or she originally received placebo) per Section 8.16, the study team will become unblinded to the participant's original study intervention allocation.

For the group of 30 existing Phase 3 participants 18 to 55 years of age who will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the sponsor will not be.

The study will be unblinded in stages once all ongoing participants either have been individually unblinded or have concluded their 6-month post–Dose 2 study visit, as follows:

- Phase 1 (after Visit 8).
- Phase 2/3, ≥16 years (after Visit 4).
- Phase 3, 12 to 15 years (after Visit 4).
- Original Phase 3 participants rerandomized to assess boostability and protection against emerging VOCs (after Visit 306).

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

Instructions on how to unblind participants ahead of administration of BNT162b2 to placebo recipients, or for other, nonemergency reasons, will be provided separately: this unblinding will NOT be performed in the IRT. The date (that the participant becomes aware of study intervention allocation) and reason that the blind was broken must be recorded in the source documentation and CRF.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants). In addition, for Phase 1 participants who go on to receive a third dose of BNT162, concomitant vaccinations will be collected from the time the participant provides informed consent (for receipt of Vaccination 3) through and including Visit 8c (1 month after the third dose). For BNT162-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to the time the participant provides informed consent (for participation in the subset) through and including Visit 306. For BNT162b2-naïve participants, the subset for evaluation of protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to study enrollment through and including Visit 405.

- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 and from 28 days prior to Visit 8a to Visit 8c for Phase 1 participants, and from 28 days prior to enrollment to Visit 3 for Phase 2/3 participants). Use is also prohibited for participants in the subset for evaluation of

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

boostability and protection against emerging VOCs, from 28 days prior to Visit 301 to Visit 303/305 and the BNT162b2-naïve participants from 28 days prior to enrollment to Visit 404.

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 2 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, for whatever reason, a participant receives only 1 dose of BNT162b2, the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. For example, because of a medication error a participant receives only 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa); the participant can return at a later date for the unscheduled visit. In this situation:

- Obtain informed consent.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Discuss contraceptive use as described in Section 10.4.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s).

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further

090177e19727636\8\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

If a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately up to: 500 mL for participants in Phase 1, 110 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum.

Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 670 mL during the 24-month study period.

For those Phase 3 participants enrolled in the subset to receive an additional dose of BNT162b2 or BNT162b2$_{SA}$, the total blood sampling volume for individual participants in this study is approximately up to 310 mL for those who receive 3 doses and 410 mL for those who receive 4 doses. Those participants in the subset who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of approximately up to 795 mL.

For those participants enrolled into the additional cohort (added as part of protocol amendment 14) of BNT162b2-naïve participants who will receive 2 doses of BNT162b2$_{SA}$, the total blood sampling volume for individual participants is approximately up to 250 mL.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof emea.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Those participants in the cohort who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of approximately up to 735 mL.

For all participants, other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

8.1.1. Efficacy Against COVID-19

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[10] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
  - Fever;
  - New or increased cough;
  - New or increased shortness of breath;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emea.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction*;
  - Admission to an ICU;
  - Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

8.1.2. Efficacy Against Asymptomatic SARS-CoV-2 Infection

VE against asymptomatic SARS-CoV-2 infection will be evaluated in 2 ways: through impact on seroconversion of N-binding antibody and impact on NAAT-confirmed SARS-CoV-2 infection, in originally enrolled Phase 2/3 participants not suffering from COVID-19. Data from participants who receive more than 2 doses of BNT162b2 will not be included after they receive a third dose.

8.1.2.1. Seroconversion of N-Binding Antibody

Blood samples for assessment of N-binding antibodies are drawn at multiple scheduled visits. An asymptomatic case of SARS-CoV-2 infection based on seroconversion of N-binding antibody is defined as positive N-binding antibody at a post–Dose 2 visit in participants without serological evidence of infection (determined by negative N-binding antibody) at Visit 1 or virological evidence of infection (determined by negative NAAT result at Visit 1 and Visit 2 and at the time of a potential COVID-19 illness). The requirement for a negative NAAT result at Visit 2 is to focus on assessment of protection against asymptomatic infection after 2 doses of vaccine, to the extent possible in an analysis based on seroconversion of N-binding antibody, recognizing that it is not possible to identify and exclude all asymptomatic infections that occur after Dose 1 and prior to Dose 2.

A secondary definition will be applied without the requirement for a negative NAAT result at Visit 2 to allow assessment of protection after 1 dose of vaccine. A positive N-binding antibody at a postvaccination visit in participants with negative N-binding antibody at Visit 1 and negative NAAT results at Visit 1 and at the time of a potential COVID-19 illness is considered an asymptomatic case.

8.1.2.2. NAAT-Confirmed SARS-CoV-2 Infection

For participants who consent to participate in an intensive period of surveillance, nasal swabs will be obtained to assess SARS-CoV-2 infection by NAAT (see Section 8.1.5).

An asymptomatic case of NAAT-confirmed SARS-CoV-2 infection is defined as a positive NAAT result on a nasal swab collected during the surveillance period from participants without COVID-19 symptoms at the time the nasal swab was taken, or within 14 days after it. The onset date of the asymptomatic case is the collection date of the first nasal swab that tested positive.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
and eurocaed
090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

8.1.3. Vaccine-Induced Immunogenicity

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay (reference strain and SA variant)
- Full-length S-binding or S1-binding IgG level assay
- RBD-binding IgG level assay (Phase 1 only)

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

Additional whole blood samples of ~120 mL will be obtained from a group of up to approximately 30 participants in each 30-µg group in the subset for evaluation of boostability and protection against emerging VOCs (both BNT162b2-experienced and BNT162b2-naïve) at select sites for isolation of PBMCs. These samples will be used to describe T-cell responses to emerging VOCs and reference strains. Some of the sample may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs, for understanding the B-cell, T-cell, and antibody repertoires. A blood sample of ~5 mL for HLA typing will also be obtained. Some of the 5-mL blood sample collected for HLA typing may be used for DNA and/or RNA isolation to further characterize HLA type.

8.1.4. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine related assay work supporting vaccine programs. No testing of the participant's DNA will be performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

confidentiality is maintained and no testing of the participant's DNA is performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

8.1.5. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.6.

The nasal swabs will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2. For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with Section 8.3.2.

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Certain participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. In addition, participants 16 through 17 years of age enrolled under protocol amendment 9 and onwards will be included in the reactogenicity subset. All other participants, including those who originally received placebo and then received BNT162b2 under protocol amendment 10 and onwards, will not complete a reactogenicity e-diary but will have their local reactions and systemic events detected and reported as AEs in accordance with Section 8.3.2. Phase 1 participants who receive a third dose of BNT162b2 will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage in the reactogenicity e-diary for 7 days following administration of the study intervention. Participants in the subset for evaluation of boostability and protection against emerging VOCs (both BNT162b2-experienced and BNT162b2-naïve) will be asked to monitor and record local reactions, systemic events, and antipyretic medication use in the reactogenicity e-diary for 7 days following each administration of the study intervention.

The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[9]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the administration of the second dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

Administration of BNT162b2 at Visits 101 and 102 to pregnant participants who originally received placebo and choose to be unblinded and receive BNT162b2 may be considered if there are local or national recommendations for COVID-19 vaccination of pregnant women, and the investigator and participant are in agreement. This overrides the requirements stated in the previous paragraph, and will not be considered as a protocol deviation. However, the EDP should still be reported in accordance with Section 8.3.5.1.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Additionally, for those participants who originally received placebo but go on to receive BNT162b2 at Vaccinations 3 and 4, AEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) through and including Visit 103. SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) to approximately 6 months after the second dose of BNT162b2 (Visit 104).

For Phase 1 participants who go on to receive a third dose of BNT162, AEs and SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccination 3) through and including Visit 8c (1 month after the third dose).

For BNT162b2-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, AEs will be collected from the time the participant provides informed consent (for participation in the subset) through and including Visit 303 for those receiving 1 additional dose and Visit 305 for those who receive 2 additional doses. For both schedules, this equates to collection for up to 1 month after the last dose. SAEs will be collected from the time the participant provides informed consent (for participation in the subset) through and including Visit 306 (5 or 6 months after the last dose, depending upon group).

For BNT162b2-naïve participants, the subset for evaluation of protection against emerging VOCs, AEs will be collected from the time the participant provides informed consent through and including Visit 404 (1 month after the second dose). SAEs will be collected from the time the participant provides informed consent through and including Visit 405 (6 months after the second dose).

090177e19727636\8\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:

  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.

  - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose of study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu/
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.6. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.6.1. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

8.3.7. Cardiovascular and Death Events

Not applicable.

8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.9. Adverse Events of Special Interest

Not applicable.

8.3.9.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

8.3.10. Medical Device Deficiencies

Not applicable.

8.3.11. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Some of the blood samples collected for PBMC isolation and HLA typing may be used for DNA and/or RNA isolation. The DNA and/or RNA samples from the PBMC isolation may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs, for understanding the B-cell, T-cell, and antibody repertoires. The DNA and/or RNA samples from the blood sample for HLA typing may be used to further characterize HLA type.

See Appendix 9 for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

Unless stated otherwise, all study visits are intended to be conducted in person at the study site. If this is not possible, because of local circumstances related to the COVID-19 pandemic, study procedures that do not require in-person participant contact may be performed by telehealth. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Irrespective of the nature of the contact, all visit procedures are expected to be performed on the same day.

As the protocol design includes visits of an unplanned nature, multiple visits may occur on the same day, but all procedures for all visits must be conducted (including collection of all blood samples).

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.5.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.

- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof are not the European Medicines Agency

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 100 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Between Visits 8 and 9

All participants who have not already been unblinded, no later than at the approximate time participants in Phase 2/3 reach Visit 4, will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, he or she will move to the procedures in Section 8.16.

8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of a third dose of BNT162, his or her next visit should be Visit 9.

- Confirm that the participant originally received 10-µg, 20-µg, or 30-µg doses of BNT162b1 or BNT162b2 at Vaccinations 1 and 2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Record nonstudy vaccinations as described in Section 6.5.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 2, 3, and 6 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer a 30-µg dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
    - Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
    - Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):
        - Fever ≥39.0°C (≥102.1°F)
        - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)
        - Severe pain at the injection site
        - Any severe systemic event
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.

- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
    - Severe pain at the injection site.
    - Any severe systemic event.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.

- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

- If Visit 3 is being conducted under amendment 12 onward: If the participant is eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, determine if he/she is willing to receive BNT162b2 as part of the study. If so, unblind the participant's study intervention assignment, and move placebo recipients to the procedures in Section 8.16.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- If not already unblinded, unblind the participant's study intervention assignment, and move placebo recipients willing to receive BNT162b2 to the procedures in Section 8.16.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;

- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination (either as part of this study, co-enrolled C459 studies, or the B7471026 [20vPnC] study), potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;

- Fever;

- New or increased cough;

- New or increased shortness of breath;

- Chills;

This document cannot be used to support any marketing authorization application and any extensions or variations thereof

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
  - Symptoms and signs, including
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
    - Significant acute renal, hepatic, or neurologic dysfunction

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

- Clinical diagnosis
- Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.
- Full blood count
- Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
- Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
- Number and type of any healthcare contact; duration of hospitalization and ICU stay
- Death

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

Prior to protocol amendment 16, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol; however, data collected from convalescent visits that occurred prior to protocol amendment 16 will remain part of the study data set.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).

- An alert in the event that the participant is hospitalized.

- Visit reminders.

- Messages of thanks and encouragement from the study team.

- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

8.15. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 or 14 days after receipt of the second dose, depending on the objective) of past SARS-CoV-2 infection.

- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

- Asymptomatic SARS-CoV-2 infection surveillance visits: To determine the incidence of asymptomatic SARS-CoV-2 infection.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, asymptomatic SARS-CoV-2 infection surveillance visit swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result, either asymptomatic or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result), prior to Visit 2 should receive Vaccination 2 as normal.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

If a participant becomes eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study.

Placebo recipients who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Dose 2, and will follow the procedures listed in this section for the remainder of their participation in the study. For Phase 2/3 participants, Visit 101 could occur at the same time as the original Visit 4.

8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant originally received only placebo at Vaccination 1/2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 4 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101)

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Record AEs as described in Section 8.3.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record AEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 103 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 104 (if any).
- Request the return of the participant's e-diary or assist the participant/participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Inform the participant/participant's parent(s)/legal guardian that his or her study participation has ended.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg)

The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 or a third and potentially a fourth dose of prototype BNT162b2$_{SA}$.

8.17.1. Visit 301 – Vaccination 3: (150 to 210 Days After Visit 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of a third dose of BNT162b2, he or should remain on the Phase 2/3 visit schedule.

Note: This visit can occur on the same day as Visit 4, but all procedures for both visits must be conducted (including collection of all blood samples).

- Confirm that the participant originally received BNT162b2 at Vaccinations 1 and 2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Record nonstudy vaccinations as described in Section 6.5.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 1, 2, 3, 5, and 6 are met and exclusion criteria 1, 3, 5, 8, 10, 11, 12, 13, 15, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. **The IRT system will also assign an additional single participant number; this number will not be used as the primary identifier for the participant, but must be included in the participant's source documents and transcribed into the CRF**. The system will also identify those participants who are to receive a fourth dose; this should be kept blinded until from the participant until Visit 303.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):

  - Fever ≥39.0°C (≥102.1°F)

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)

  - Severe pain at the injection site

  - Any severe systemic event

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.17.2. Visit 302 – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 301)

- Record AEs as described in Section 8.3.

- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.3. Visit 303 – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 301)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.

Only if the participant is to receive a further dose of BNT162b2$_{SA}$:

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 1, 2, 3, 5, and 6 are met and exclusion criteria 1, 3, 5, 8, 10, 11, 12, 13, 15, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):
  - Fever ≥39.0°C (≥102.1°F)
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)
  - Severe pain at the injection site
  - Any severe systemic event
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc europaea

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.4. Visit 304 – 1-Week Follow-up Visit (Vaccination 4): (6 to 8 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.5. Visit 305 – 1-Month Follow-up Visit (Vaccination 4): (28 to 35 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.6. Visit 306 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 301):

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.17.7. Visit 307 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 301):

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record latest CD4 count and HIV viral load.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.18. Administration of BNT162b2$_{SA}$ to BNT162b2-naïve Participants

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

8.18.1. Visit 401 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Obtain any medical history of clinical significance.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - Provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
    - Severe pain at the injection site.
    - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the study intervention accountability records.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.18.2. Visit 402 – Vaccination 2: (19 to 23 Days After Visit 401)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the study intervention accountability records.

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.18.3. Visit 403 – 1-Week Follow-up Visit (After Vaccination 2): (6 to 8 Days After Visit 402)

- Record AEs as described in Section 8.3.

- Record nonstudy vaccinations as described in Section 6.5.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.18.4. Visit 404 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.18.5. Visit 405 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

8.18.6. Visit 406 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 402)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.19. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11 until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The surveillance will be conducted per the procedures listed below.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

8.19.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11

Before surveillance begins and any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The visit should be conducted only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1) and this visit should be temporarily delayed until the symptoms have resolved.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 3 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Record AEs as described in Section 8.3 (only if the participant remains in the AE reporting period; see Section 8.3.1).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Ask the participant to obtain a surveillance self-swab at home in approximately 14 days or schedule an appointment for the participant to return to collect the swab at the site. The swab should be collected only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.19.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection

This is a repeating swab collection and will be conducted approximately every 14 days until the intensive surveillance period ends.

- Participant collects a self-swab and ships it to the site for assessment at the central laboratory. The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- Complete the source documents with the swab information.

- The investigator or an authorized designee completes the CRFs with the swab information.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by all-available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either VE_1 >30% or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated based on the lower bound of the 95% CI. VE will be demonstrated if the lower bound of the 2-sided 95% CI for VE is >20%.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

9.1.2.2.1. Hypothesis for Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2**.** If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

9.1.2.2.2. Hypotheses for Boostability and Protection Against Emerging SARS-CoV-2 VOCs

The primary and secondary objectives for boostability and protection against emerging VOCs for BNT162b2-experienced participants and BNT162b2-naïve participants will be assessed based on:

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

- GMRs of SARS-CoV-2 SA and/or reference strain neutralizing titers using a 1.5-fold noninferiority margin. Noninferiority is met if the lower limit of the alpha adjusted CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.8.

- The difference in percentages of participants with seroresponse to SA and/or reference strain using a 10% noninferiority margin. Noninferiority is met if the lower limit of the alpha-adjusted CI for the difference in percentages of participants with seroresponse is >-10%.

Seroresponse is defined as achieving ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

9.1.2.2.2.1. Multiplicity Control for the Boostability and Protection-Against-VOCs Objectives

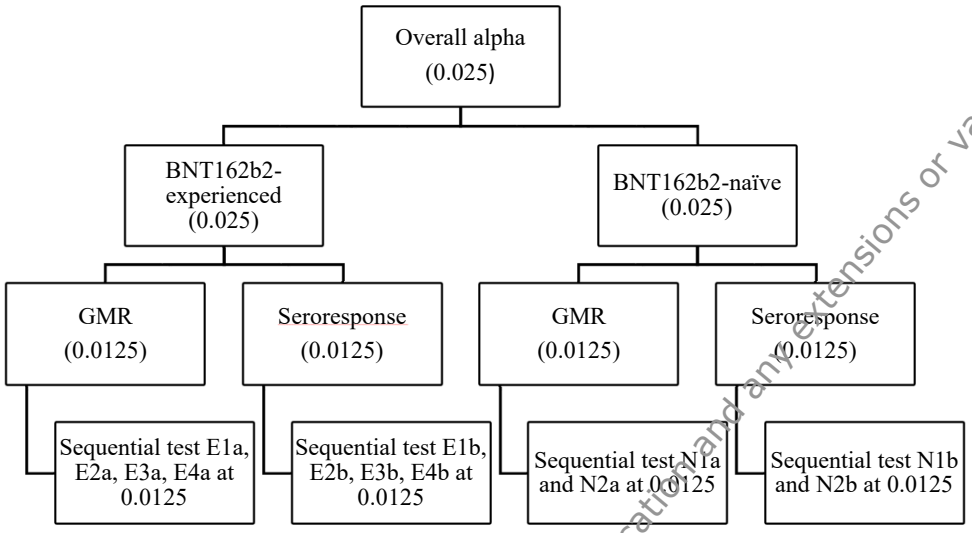
Figure 1 outlines the type I error control strategy for multiple objectives across different populations (BNT162b2-experienced or BNT162b2-naïve) and estimands (GMR or seroresponse).

The objectives for BNT162b2-experienced participants and BNT162b2-naïve participants will be evaluated independently. The vaccine-experienced and -naïve individuals are different populations with different objectives. The 2 populations are included in the same study to improve operational efficiency. Therefore, no type I error adjustments will be applied to the assessments of the 2 populations.

For each population, the objectives will be evaluated separately for each estimand. To control the overall type I error, the 1-sided alpha of 0.025 will be split and allocated equally to each estimand. Specifically, for each estimand, the hypotheses will be tested in sequential order (as listed in the objectives in Section 3) using a 1-sided alpha of 0.0125 (Figure 1, where E and N represent vaccine-experienced and vaccine-naïve, respectively, and a and b represent GMR and seroresponse estimands, respectively).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Figure 1. Multiplicity Schema



9.2. Sample Size Determination

9.2.1. Phase 1

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

9.2.2. Efficacy Against COVID-19

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

9.2.3. Efficacy Against Asymptomatic Infection

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection will be assessed in Phase 2/3 participants (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT). Assuming a true VE of 70%, a total of 53 asymptomatic cases will provide approximately 90% power to conclude true VE >20%. A total of 206 cases is needed to have 90% power if the true VE is 50%. The hypothesis for asymptomatic seroconversion of N-binding antibody will be tested if at least 206 cases are accrued. The hypothesis for asymptomatic infection based on central laboratory–confirmed NAAT in participants who are consented to participate in the intensive surveillance phase will be tested if at least 53 cases are accrued.

9.2.4. Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 280 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.65	-0.2	225	90.4%

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer.
a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).
b. At 0.05 alpha level (2-sided).

9.2.5. Boostability and Protection Against Emerging SARS-CoV-2 VOCs

To assess boostability and protection against emerging SARS-CoV-2 VOCs, approximately 300 participants will be enrolled in each of the 3 groups (BNT162b2-experienced participants to receive either a third dose of BNT162b2 at 30 µg [Group 1] or a third dose of BNT162b2$_{SA}$ [Group 2], BNT162b2-naïve participants to receive 2 doses of BNT162b2$_{SA}$ [Group 3]) to provide an acceptable safety database.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

Assuming 20% nonevaluable rate, approximately 240 evaluable participants in each group will contribute to immunogenicity evaluation. This will provide sufficient power for noninferiority evaluations with appropriate multiplicity adjustment for type I error control.

For comparisons based on GMR, the assay standard deviation in log scale is assumed to be 0.74 based on results from Phase 2 of the study and adjusted for assay variability. A GMR of 1 is assumed for each comparison.

For comparisons based on seroresponse, a 90% response rate is assumed for each comparative group or at each comparative time point.

Within-Group Comparison for BNT162b2-Experienced Participants

For each randomized group of BNT162b2-experienced participants (Group 1: received a third dose of BNT162b2 at 30 μg and Group 2: received a third dose of $BNT162b2_{SA}$), with 240 evaluable participants and the stated assumptions for the GMR and standard deviation, the study has >99.9% power to demonstrate NI based on GMR for the objectives in vaccine-experienced individuals using a 1.5-fold margin.

Assuming true response rate of 90% in each group, the study has 89.7% power to show NI based on seroresponse rate for the objectives in vaccine-experienced individuals using a 10% margin.

Between-Group Comparison of BNT162b2-Naïve Participants to Selected Existing Phase 3 Participants Who Received 2 Doses of BNT162b2

Approximately 300 participants will be selected from the existing Phase 3 participants who received 2 doses of BNT162b2 to form the control group for the BNT162b2-naïve participants. The selection will ensure comparable distribution of age, sex, and other demographic factors in the control group and BNT162b2-naïve group. With 240 evaluable BNT162b2-naïve participants and 240 evaluable participants in the control group and the above stated assumptions for the GMR, standard deviation, and seroresponse rate, the study has >99.9%% power to declare NI based on GMR for the objectives in vaccine-naïve individuals using a 1.5-fold margin and 89.7% power to declare NI based on seroresponse rate using a 10% margin.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

9.2.6. Safety

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=300	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.03	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.06	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.11	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.16	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.21	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.26	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.36	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.45	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.53	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.59	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.65	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.78	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	0.95	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 3 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 (or BNT162b1 for Phase 1) as initially randomized, with Dose 2 received within the predefined window, receive a third dose of BNT162b2 or BNT162b2$_{SA}$ as rerandomized (or receive a third dose of BNT162b2 for Phase 1), have at least 1 valid and determinate immunogenicity result after Dose 3 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 4 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 as initially randomized, with Dose 2 received within the predefined window, receive 2 booster doses of BNT162b2$_{SA}$ as rerandomized, have at least 1 valid and determinate immunogenicity result after Dose 4 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emea-eropaed
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Population	Description
Dose 3 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 (or BNT162b1 for Phase 1) at initial randomization, receive a third dose of BNT162b2 or BNT162b2$_{SA}$ at rerandomization (or receive a third dose of BNT162b2 for Phase 1), and have at least 1 valid and determinate immunogenicity result after Dose 3.
Dose 4 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 at initial randomization, receive 2 booster doses of BNT162b2$_{SA}$ at rerandomization, and have at least 1 valid and determinate immunogenicity result after Dose 4.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
Evaluable efficacy (seroconversion)	All eligible randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window, have at least 1 N-binding antibody test result available at a post–Dose 2 visit, and have no other important protocol deviations as determined by the clinician prior to the first post–Dose 2 N-binding antibody test.
Evaluable efficacy (asymptomatic surveillance)	All eligible randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window, consent to participate in the asymptomatic surveillance, and have no other important protocol deviations as determined by the clinician on or before the start of the asymptomatic surveillance period.
All-available efficacy	Dose 1 all-available: All randomized participants who receive at least 1 vaccination. Dose 2 all-available: All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention. Analyses of reactogenicity endpoints will be based on a subset of the safety population that includes participants with any e-diary data reported after vaccination.
Booster safety	All participants who receive at least 1 booster dose of the study intervention.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Empirical RCDCs will be provided for all immunogenicity analyses.

Endpoint	Statistical Analysis Methods
Primary immunogenicity (Phase 3, boostability and protection against emerging VOCs)	In order to allow direct comparability with the reference strain, the anti-SA NTs may be adjusted to account for intrinsic variant or assay characteristics. The small group of existing Phase 3 participants who are to receive a third and fourth dose of BNT162b2$_{SA}$ will not be included in the primary and secondary analyses except for the last secondary descriptive objective. ***BNT162b2-Experienced Participants:*** **E1a: GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 in the same individuals** **E2a: GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** The comparisons of different NTs (anti-SA or anti–reference strain) or the same NTs at different time points within the same group will be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Endpoint	Statistical Analysis Methods
	limited to participants with nonmissing values at both time points or both NT measurements. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (eg, later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 97.5% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. Noninferiority of E1a and E2a will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8. **E1b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2 in the same individuals** **E2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** The percentages of participants with seroresponse at each time point and the difference in percentages will be provided. The 2-sided 97.5% CIs for the difference in percentages of participants with seroresponse will be calculated using the Miettinen and Nurminen method. Noninferiority of E1b and E2b will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%. ***BNT162b2-Naïve Participants:*** **N1a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2** For the between-group comparison, GMRs will be calculated as the mean of the difference of logarithmically transformed assay results between 2 groups and exponentiating the mean. The associated 2-sided 97.5% CIs will be obtained by calculating CIs using Student's

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Endpoint	Statistical Analysis Methods
	t-distribution for the mean difference of the logarithmically transformed titers and exponentiating the confidence limits. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8. **N1b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2** The difference in percentages of participants with seroresponse and associated 2-sided 97.5% CIs will be calculated in the same way as for primary endpoints E1b and E2b. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%.
Secondary immunogenicity (Phase 3, boostability and protection against emerging VOCs)	***BNT162b2-Experienced Participants:*** **E3a: GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** **E4a: GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 in the same individuals** **E3b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** **E4b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2 in the same individuals** GMRs and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1a and E2a. If noninferiority of E1a and E2a are both established, E3a and E4a will be assessed sequentially using the same criterion (lower bound of the

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Endpoint	Statistical Analysis Methods
	2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8). The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. Similarly, if noninferiority of E1b and E2b are both established, E3b and E4b will be assessed sequentially using the same criterion (lower bound of the 2-sided 97.5% CI for the difference in percentages is greater than -10%). **GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg** **The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. **GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** **The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint E1a and E2a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints E1b and E2b.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	BNT162b2-Naïve Participants: **N2a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2** **N2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2** GMR and the associated 2-sided 97.5% CI will be calculated in the same way as for the primary endpoint N1a. Statistical superiority of N2a will be assessed if noninferiority of N1a is established. Superiority of N2a will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 1. The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. Statistical superiority of N2b will be assessed if noninferiority of N1b is established. Superiority of N2b will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than 0%. **GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2** **The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints E1b and E2b
Secondary immunogenicity (Phase 1)	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Endpoint	Statistical Analysis Methods
	provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Endpoint	Statistical Analysis Methods
	The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the 16- to 25-year age group)	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and 2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment. The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Endpoint	Statistical Analysis Methods
	difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2: **GMTs/GMCs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level** GMTs/GMCs and 2-sided 95% CIs will be provided by initial vaccine and age group for the following time points: • At Dose 3 and 7 days and 1 month after Dose 3 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level** GMFRs from before Dose 3 to 7 days and 1 month after Dose 3 and 2-sided 95% CIs will be provided by initial vaccine and age group. GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Endpoint	Statistical Analysis Methods
	logarithmically transformed assay results and exponentiating the confidence limits. **GMRs of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2** GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed reference-strain titers for each participant (1 month after Dose 3 – 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. **GMRs of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2** GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (SA-variant titer at 1 month after Dose 3 – reference-strain titer at 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.
Exploratory immunogenicity (Phase 2/3)	**GMTs/GMCs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Endpoint	Statistical Analysis Methods
	mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels after Dose 1 and after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Endpoint	Statistical Analysis Methods
Exploratory immunogenicity (Phase 3, boostability and protection against emerging VOCs)	**GMTs of SARS CoV-2 reference strain neutralizing titers in participants receiving a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$** GMTs and associated 2-sided 95% CIs at Dose 3 and each subsequent time point will be provided for each vaccine group and age group. **GMFRs of SARS CoV-2 reference strain neutralizing titers in participants receiving a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$** GMFRs from Dose 3 to each subsequent time point and associated 2-sided 95% CIs will be provided for each vaccine group and age group. **Geometric mean NT for any VOC not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2** Geometric means and associated 2-sided 95% CIs of any anti-VOC neutralizing titers will be provided at each time point for each group.

9.4.2. Efficacy Analyses

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Endpoint	Statistical Analysis Methods
	Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.
Secondary	**First: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Second: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Third and fourth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Endpoint	Statistical Analysis Methods
	Fifth and sixth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints for COVID-19 illness according to CDC-defined symptoms will be evaluated descriptively with 95% CIs. **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days or from 14 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[10] Missing efficacy data will not be imputed. The following secondary efficacy endpoints regarding asymptomatic SARS-CoV-2 infection will be evaluated based on a success criterion of the lower bound of the 2-sided 95% CI for VE being >20%. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past**

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
the European Economic Area
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Endpoint	Statistical Analysis Methods
	SARS-CoV-2 infection or confirmed COVID-19 for the active vaccine group to the placebo group VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate per 1000 person-years of follow-up in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The hypothesis will be tested if at least 206 cases are accrued. In addition, a descriptive summary of VE against asymptomatic infection over different time intervals (ie, prior to 1 month after Dose 2, from 1 month after Dose 2 onward), along with the associated 2-sided 95% CI, will be calculated using the same method. The analysis of the primary definition of asymptomatic cases will be based on the evaluable efficacy (seroconversion) population and the Dose 2 all-available efficacy population. The analysis of the secondary definition of asymptomatic cases will be based on the Dose 1 all-available efficacy population. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants without evidence of infection (up to the start of asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The hypothesis will be tested if at least 53 cases are accrued. The analysis will be based on the evaluable efficacy (asymptomatic surveillance) population and the all-available efficacy population and will include only participants who are consented to participate in the asymptomatic surveillance and who do not have serological or virological evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.ea

Endpoint	Statistical Analysis Methods
Exploratory	**Ratios of confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants without, and with and without, evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** After the primary objectives are met at the final analysis of at least 164 first primary cases, the study will continue with blinded follow-up until the participant is unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. A descriptive update of VE will be provided with additional follow-up data. VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[10] Supportive analysis of time to confirmed COVID-19 illness will be performed using Kaplan-Meier cumulative incidence curves. Participants who were randomized to placebo will be censored at the time of receipt of BNT162b2. **Incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness from 7 days after the second dose will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted. **Incidence of asymptomatic SARS-CoV-2 infection through the entire study follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants who received BNT162b2 and who have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for asymptomatic infection will be provided for participants who received BNT162b2 at initial randomization and have no serological or

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	virological evidence of past SARS-CoV-2 infection or confirmed COVID-19. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with evidence of infection (up to the start of the asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. Participants who are consented to participate in the asymptomatic surveillance and who have serological or virologic evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period will be included in the analysis.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[11] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group. AEs and SAEs reported during the open-label follow-up period will be summarized separately for participants who were unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. For Phase 3 participants enrolled for assessment of boostability and protection against emerging VOCs, descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for local reactions and systemic events from Day 1 through Day 7 after each dose, AEs from Dose 1 to 1 month after the last dose, and SAEs from Dose 1 to 5 or 6 months after the last dose. Local reactions and systemic events from Day 1 through Day 7 after each dose will be presented by severity and cumulatively across severity levels. The safety analyses after the first dose and after booster dose(s) are based on the safety population and booster safety population, respectively. Analyses of reactogenicity endpoints are based on a subset of the safety population that includes participants with any e-

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
https://ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Endpoint	Statistical Analysis Methods
	diary data reported after vaccination. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2: Descriptive statistics will be provided by initial vaccine and age group for local reactions and systemic events from Day 1 through Day 7 after Dose 3, and AEs/SAEs from Dose 3 to 1 month after Dose 3. Local reactions and systemic events from Day 1 through Day 7 after Dose 3 will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs.

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" and each lot of "Process 2" will be summarized descriptively. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected randomly for the analysis.

Exploratory analyses to investigate possible immunological correlates with efficacy, and characterization of infecting SARS-CoV-2 variants, may be conducted.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

The cell-mediated immune response and additional humoral immune response parameters to the reference strain and SA will be summarized for the subset of participants with PBMC samples collected.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 6 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support and marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8, for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

Only the first primary endpoint will be analyzed at IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints (confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and in all participants, confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection and in all participants) will be evaluated sequentially in the stated order, by the same method used for the evaluation of primary VE endpoints. Success thresholds for secondary VE endpoints will be appropriately chosen to control overall type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Complete safety and immunogenicity analysis approximately 1 month after Dose 3 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

(with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.

- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.

- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.

- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2.

- Safety analyses approximately 1 month after Dose 3 for Phase 3 participants included in the booster evaluation (30 µg or low-dose booster) and approximately 1 month after Dose 2 for newly enrolled Phase 3 participants included in the BNT162b2$_{SA}$ evaluation.

- Immunogenicity analyses approximately 1 month after Dose 3 for Phase 3 participants included in the booster evaluation (30 µg or low-dose booster) and approximately 1 month after Dose 2 for newly enrolled Phase 3 participants included in the BNT162b2$_{SA}$ evaluation, when serology data for the reference strain or for the SA strain are available.

- Analysis of efficacy against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) when a sufficient number of cases have accrued to evaluate the objective(s).

- Complete safety and efficacy analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.

- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met
- Review of safety and/or immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review
- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Up until the final efficacy analysis, 3 blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial. When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc.europa.eu

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
20vPnC	20-valent pneumococcal conjugate vaccine
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCR	B-cell receptor
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
E1, E2, etc	vaccine-experienced (statistical tests)
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Abbreviation	Term
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof in the European Union

Abbreviation	Term
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N1, N2, etc	vaccine-naïve (statistical tests)
N/A	not applicable
NAAT	nucleic acid amplification test
NI	noninferiority
non-S	nonspike protein
NT	neutralizing titer
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SA	South Africa
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Abbreviation	Term
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
TCR	T-cell receptor
UK	United Kingdom
ULN	upper limit of normal
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
VOC	variant of concern
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs after accrual of at least 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.9. Appendix 9: Genetics

Use/Analysis of DNA and/or RNA

- Genetic variation may impact a participant's response to study intervention, as well as susceptibility to and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA and/or RNA analysis.
- The results of genetic analyses may be reported in a CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA and/or RNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
  - Samples for specified genetic analysis (see Section 8.7) will be stored for up to 15 years or other period as per local requirements.
- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.

4 Centers for Disease Control and Prevention. Emerging SARS-CoV-2 variants. Available from: https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html. Updated: 28 Jan 2021. Accessed: 10 Feb 2021.

5 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

6 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

7 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

8 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

9 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

10 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

11 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e197276368\Approved\Approved On: 28-May-2021 17:50 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 16 Clean Copy 28May2021
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	28-May-2021 17:38:51	Business Line Approver
PPD	28-May-2021 17:50:02	Final Approval

090177e19727636\Approved\Approved On: 28-May-2021 17:50 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 15	25 March 2021	• In order to further characterize booster responses induced by BNT162b2, 2 additional lower-dose booster groups have been added to the subset for evaluation of boostability and protection against emerging VOCs. An additional 5-µg or 10-µg dose of BNT162b2 will be given to approximately 144 Phase 3 participants approximately 5 to 7 months after their second dose of BNT162b2. • To further describe cell-mediated immune responses following isolations of PBMCs in a subset of both the Phase 3 participants who receive a single booster vaccination and the BNT162b2-naïve group who receive $BNT162b2_{SA}$, additional genetic testing may also be performed; corresponding details and an appendix have been added. • An exploratory objective was added for Phase 3 participants to describe the immune response to a third dose of BNT162b2 or a third or fourth dose of $BNT162b2_{SA}$ at later time points to align with analyses and corresponding changes detailed in the statistical section. • Removed the lower age limit for eligibility for administration of BNT162b2 to those originally assigned to placebo: this will now be covered in the recommendations detailed separately, and available in the electronic study reference portal. • Allowed administration of BNT162b2 at Visits 101 and 102 to pregnant participants in certain circumstances. • To align with contraception requirements, reduced the EDP reporting period to 28 days after the last dose of study intervention.
Protocol amendment 14	02 March 2021	• In order to further describe duration of protection, and heterologous/homologous protection against the emerging VOCs, an additional dose of BNT162b2 or $BNT162b2_{SA}$ will be given to approximately 600 Phase 3 participants approximately 5 to 7 months after their second dose of BNT162b2; a further dose of $BNT162b2_{SA}$ will be given to approximately 30 of those participants who receive $BNT162b2_{SA}$: • Added corresponding objectives, estimands, and endpoints

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Added corresponding SoA and procedures • Added details in the statistical methods sections. • Approximately 300 BNT162b2-naïve participants will be enrolled and receive 2 doses of BNT162b2$_{SA}$ to describe heterologous/homologous protection against the emerging VOCs and reference strains: • Added corresponding objectives, estimands, and endpoints • Added corresponding SoA and procedures • Added details in the statistical methods sections. • Cell-mediated immune responses will also be described following isolations of PBMCs in a subset of both the Phase 3 participants who receive a single booster vaccination and the BNT162b2-naïve group who receive BNT162b2$_{SA}$. • Added the asymptomatic case definitions in Section 8.1 and further clarified the secondary definition for asymptomatic case based on seroconversion of N-binding antibody. • Defined the analysis populations used for evaluation of asymptomatic infection based on seroconversion of N-binding antibody and based on NAAT from participants who consent to active surveillance. • Clarified that unblinding for a nonemergency reason should be conducted outside of the IRT system. • Clarified that if multiple visits occur on the same day, all procedures for all visits must be conducted (including collection of all blood samples). • Clarified the plan for stepwise unblinding of the sponsor in the study.
Protocol amendment 13	12 February 2021	• In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2: • Added corresponding objectives, estimands, and endpoints • Added corresponding SoA and procedures

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Added details in the statistical methods sections. • Clarified the population used for analysis of reactogenicity endpoints. • To align with current recommendations, investigators may exercise judgment on review of inclusion and exclusion criteria ahead of vaccination with BNT162b2 for participants who originally received placebo. • Clarified that if a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent. • Participants who provide biweekly swabs for surveillance of asymptomatic infection should now continue to swab even after unblinding if they originally received BNT162b2, to maximize the numbers of swabs to be collected. • Clarified the procedures for unscheduled visits to administer a second dose in the event a participant received only 1 dose of BNT162b2.
Protocol amendment 12	14 January 2021	• Because of a formatting error in protocol amendment 11, exclusion criterion 4 was inadvertently added to exclusion criterion 3 and the subsequent criteria renumbered. This amendment corrects that error. • Because of a change in the pace with which participants ≥16 years of age who originally received placebo will become eligible for receipt of BNT162b2, text was updated throughout the protocol to reflect that this will happen in a phased manner, with recommendations detailed separately and available in the electronic study reference portal. • Clarified that participants who are unblinded because they become potentially eligible for receipt of BNT162b2 will not participate in surveillance for asymptomatic SARS CoV-2 infection. • Corrected the exploratory objective to describe non-S seroconversion to SARS-CoV-2 to clarify that this will only include participants who received BNT162b2 at initial randomization (since those who received it subsequently do not have blood drawn). • In line with current recommendations, removed the requirement to discontinue study

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		intervention because of a diagnosis of COVID-19 during the study.
Protocol amendment 11	04 January 2021	• Added approaches to evaluate efficacy against asymptomatic SARS-CoV-2 infection: • Added objectives, estimands, and endpoints, and statistical methods, for assessment via N-binding antibody seroconversion; • Added a potential intensive surveillance period for nasal swabbing, for assessment via NAAT: • Corresponding objectives, estimands, and endpoints added • Corresponding SoA and procedures added • Details added in the statistical methods sections. • Added the possibility of assessing full-length S-binding, instead of S1-binding, IgG levels in Phase 2/3. • Clarified in Section 4.1.1 that any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity at the approximate time participants in Phase 2/3 reach Visit 4, for consistency with other sections. • Added a sentence to reflect that assent is obtained from participants <18 years of age.
Protocol amendment 10	01 December 2020	• Added the possibility of administering BNT162b2 to participants who originally received placebo, following any local or national recommendations. • Added the possibility of administering BNT162b2 to participants who originally received placebo, following completion of the active safety surveillance period. • Added corresponding exploratory objectives and statistical analysis details. • Removed immunogenicity analyses of titers greater than defined threshold(s). • Removed the need for blinded COVID-19 case review after the final efficacy analysis. • Included the possibility, due to local circumstances related to the COVID-19 pandemic, that study procedures that do not require in-person participant contact may be performed by telehealth. • In light of additional information to better estimate the standard deviation of SARS-CoV-2 neutralizing titers, increased the sample size for

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		the noninferiority immunogenicity analysis in adolescents 12 to 15 years of age.
Protocol amendment 9	29 October 2020	• To better align with the natural history of SARS-CoV-2 infection, added Phase 2/3 secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days after the second dose; also modified the existing secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days, as well as 7 days, after the second dose; • Made corresponding changes to the study design, study assessments and procedures, and statistical analysis sections. • For operational reasons, removed the interim analysis planned after accrual of 32 cases. • Clarified that interim analyses will be conducted after accrual of *at least* 62, 92, and 120 cases. • Included any participants 16 through 17 years of age enrolled under this amendment in the reactogenicity subset. • Added an unblinded clinical scientist to support DMC activities. • Clarified that serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.
Protocol amendment 8	15 October 2020	• Removed "N-binding antibody" and "SARS-CoV-2 detection by NAAT" as endpoints from the third exploratory objective, as these results are used for the determination of the population, and are not endpoints. • Clarified that the "Process 1" participants included in the descriptive analysis of "Process 1"- and "Process 2"-manufactured study interventions will be selected randomly. • Clarified that surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study. • Further modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Clarified that for participants who are not in the reactogenicity subset, local reactions and systemic events following vaccination should be detected and reported as AEs. • Clarified that premenarchal females are not WOCBP.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2. • Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2." • Clarified the degree of unblinding on the unblinded submissions team in Section 6.3.3. • Made provision for a second dose of BNT162b2 in participants who were affected by a medication error at Visit 2 in Section 6.6. • Provided further clarification regarding discontinuation of study intervention in Section 7.1. • Modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Added that 2 periods of potential COVID-19 symptoms within 4 days will be considered as a single illness. • Provided guidance in Section 8.13 regarding circumstances in which a SARS-CoV-2 test might be required even if symptoms within 7 days following each vaccination are considered more likely due to vaccine reactogenicity. • Made allowance in Section 8.13 for a second SARS-CoV-2 test to be performed within the same potential COVID-19 illness if it is in accordance with routine practice. • Added Section 8.15 to describe the reporting of SARS-CoV-2 test results and their implications for participants receiving a second vaccine dose. • Added statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age. • Amended scope of analyses of safety data in Section 9.5.1.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Made various editorial changes.
Protocol amendment 6 (Germany-specific)	23 September 2020	• According to regulatory request, inclusion criterion 1 now specifies that participants less than 18 years of age will not be enrolled in the EU.
Protocol amendment 6	08 September 2020	• Reordered some procedures in the Phase 2/3 schedule of activities for consistency with the main body of the protocol. • Corrected the window for the 6-month follow-up visit to be approximately 6 months after Vaccination 2. • Reduced the volume of blood draws to ~20 mL. • Removed the need to have safety data reported for participants to be included in the safety objective assessment. • Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease. • Increased the sample size for Phase 2/3 to ~43,998. • Clarified that inclusion criterion 4 (ie, participants at higher risk for acquiring COVID-19) is applicable for Phase 2/3 only, and provided some examples. • Removed exclusion criterion 2 (ie, known infection with HIV, HCV, or HBV) for Phase 3 and added criteria for HIV-positive participants. • Decreased the lower age limit and removed the upper age limit for inclusion in Phase 2/3 in order to evaluate BNT162b2 30 µg in older adolescents and those over 85 years of age; updated the title and other references to adults to align with this change. • Renamed the immunological assays to align with other program-level documents. • Removed reference to the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) being “heads up.” • Clarified that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention. • Added clarification that potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. • Updated the analysis population descriptions to align with the study SAP.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory. • Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7. • Updated the stopping and alert rule parameters for enhanced COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 22
LIST OF FIGURES 22
1. PROTOCOL SUMMARY 23
1.1. Synopsis 23
1.2. Schema 37
1.3. Schedule of Activities 38
1.3.1. Phase 1 38
1.3.2. Phase 2/3 45
1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo 49
1.3.4. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) 51
1.3.5. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants 54
1.3.6. Surveillance for Asymptomatic SARS-CoV-2 Infection 57
2. INTRODUCTION 58
2.1. Study Rationale 58
2.2. Background 58
2.2.1. Clinical Overview 60
2.3. Benefit/Risk Assessment 60
2.3.1. Risk Assessment 62
2.3.2. Benefit Assessment 64
2.3.3. Overall Benefit/Risk Conclusion 64
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 64
3.1. For Phase 1 64
3.2. For Phase 2/3 66
4. STUDY DESIGN 73
4.1. Overall Design 73
4.1.1. Phase 1 74
4.1.2. Phase 2/3 75
4.2. Scientific Rationale for Study Design 78
4.3. Justification for Dose 78

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

4.4. End of Study Definition 79
5. STUDY POPULATION 80
5.1. Inclusion Criteria 80
5.2. Exclusion Criteria 81
5.3. Lifestyle Considerations 84
5.3.1. Contraception 84
5.4. Screen Failures 84
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 84
6. STUDY INTERVENTION 85
6.1. Study Intervention(s) Administered 86
6.1.1. Manufacturing Process 86
6.1.2. Administration 87
6.2. Preparation/Handling/Storage/Accountability 87
6.2.1. Preparation and Dispensing 88
6.3. Measures to Minimize Bias: Randomization and Blinding 89
6.3.1. Allocation to Study Intervention 89
6.3.2. Blinding of Site Personnel 89
6.3.3. Blinding of the Sponsor 90
6.3.4. Breaking the Blind 91
6.4. Study Intervention Compliance 91
6.5. Concomitant Therapy 92
6.5.1. Prohibited During the Study 92
6.5.2. Permitted During the Study 93
6.6. Dose Modification 93
6.7. Intervention After the End of the Study 94
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 94
7.1. Discontinuation of Study Intervention 94
7.2. Participant Discontinuation/Withdrawal From the Study 95
7.2.1. Withdrawal of Consent 96
7.3. Lost to Follow-up 96

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8. STUDY ASSESSMENTS AND PROCEDURES 96
8.1. Efficacy and/or Immunogenicity Assessments 98
8.1.1. Efficacy Against COVID-19 98
8.1.2. Efficacy Against Asymptomatic SARS-CoV-2 Infection 100
8.1.2.1. Seroconversion of N-Binding Antibody 100
8.1.2.2. NAAT-Confirmed SARS-CoV-2 Infection 100
8.1.3. Vaccine-Induced Immunogenicity 101
8.1.4. Biological Samples 101
8.1.5. Surveillance for Asymptomatic SARS-CoV-2 Infection 102
8.2. Safety Assessments 102
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 102
8.2.2. Electronic Diary 103
8.2.2.1. Grading Scales 104
8.2.2.2. Local Reactions 104
8.2.2.3. Systemic Events 105
8.2.2.4. Fever 106
8.2.2.5. Antipyretic Medication 107
8.2.3. Phase 1 Stopping Rules 107
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 108
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 109
8.2.6. Pregnancy Testing 109
8.3. Adverse Events and Serious Adverse Events 109
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 110
8.3.1.1. Reporting SAEs to Pfizer Safety 111
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 111
8.3.2. Method of Detecting AEs and SAEs 111
8.3.3. Follow-up of AEs and SAEs 112
8.3.4. Regulatory Reporting Requirements for SAEs 112
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 112
8.3.5.1. Exposure During Pregnancy 112

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.3.6. Exposure During Breastfeeding 114
8.3.6.1. Occupational Exposure 114
8.3.7. Cardiovascular and Death Events 115
8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 115
8.3.9. Adverse Events of Special Interest 115
8.3.9.1. Lack of Efficacy 115
8.3.10. Medical Device Deficiencies 116
8.3.11. Medication Errors 116
8.4. Treatment of Overdose 117
8.5. Pharmacokinetics 117
8.6. Pharmacodynamics 117
8.7. Genetics 117
8.8. Biomarkers 117
8.9. Immunogenicity Assessments 118
8.10. Health Economics 118
8.11. Study Procedures 118
8.11.1. Phase 1 118
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 118
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 119
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 122
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 123
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 124
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 126
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 128
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 129
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4) 129
8.11.1.10. Between Visits 8 and 9 130

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2) 130
8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a)....132
8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a)....132
8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2....133
8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2....134
8.11.2. Phase 2/3....134
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 134
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 137
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)....139
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)....140
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 140
8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 141
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 142
8.13. COVID-19 Surveillance (All Participants) 143
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 144
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)....145
8.14. Communication and Use of Technology....146
8.15. SARS-CoV-2 NAAT Results....146

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo 147
8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2) 147
8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101) 149
8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102) 150
8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102) 150
8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102) 151
8.17. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg) 151
8.17.1. Visit 301 – Vaccination 3: (150 to 210 Days After Visit 2) 151
8.17.2. Visit 302 – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 301) 154
8.17.3. Visit 303 – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 301) 154
8.17.4. Visit 304 – 1-Week Follow-up Visit (Vaccination 4): (6 to 8 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$ 156
8.17.5. Visit 305 – 1-Month Follow-up Visit (Vaccination 4): (28 to 35 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$ 157
8.17.6. Visit 306 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 301): 157
8.17.7. Visit 307 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 301): 158
8.18. Administration of BNT162b2$_{SA}$ to BNT162b2-naïve Participants 158
8.18.1. Visit 401 – Vaccination 1: (Day 1) 158
8.18.2. Visit 402 – Vaccination 2: (19 to 23 Days After Visit 401) 161
8.18.3. Visit 403 – 1-Week Follow-up Visit (After Vaccination 2): (6 to 8 Days After Visit 402) 163
8.18.4. Visit 404 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 402) 163
8.18.5. Visit 405 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 402) 164

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.18.6. Visit 406 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 402) 165
8.19. Surveillance for Asymptomatic SARS-CoV-2 Infection 165
8.19.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11 166
8.19.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection 167
9. STATISTICAL CONSIDERATIONS 167
9.1. Estimands and Statistical Hypotheses 167
9.1.1. Estimands 167
9.1.2. Statistical Hypotheses 168
9.1.2.1. Statistical Hypothesis Evaluation for Efficacy 168
9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity 168
9.2. Sample Size Determination 170
9.2.1. Phase 1 170
9.2.2. Efficacy Against COVID-19 170
9.2.3. Efficacy Against Asymptomatic Infection 171
9.2.4. Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years 171
9.2.5. Boostability and Protection Against Emerging SARS-CoV-2 VOCs 171
9.2.6. Safety 173
9.3. Analysis Sets 174
9.4. Statistical Analyses 176
9.4.1. Immunogenicity Analyses 176
9.4.2. Efficacy Analyses 186
9.4.3. Safety Analyses 191
9.4.4. Other Analyses 193
9.5. Interim Analyses 194
9.5.1. Analysis Timing 196
9.6. Data Monitoring Committee or Other Independent Oversight Committee 197
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 199
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 199

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

10.1.1. Regulatory and Ethical Considerations 199
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 199
10.1.2. Informed Consent Process 200
10.1.3. Data Protection 201
10.1.4. Dissemination of Clinical Study Data 201
10.1.5. Data Quality Assurance 202
10.1.6. Source Documents 204
10.1.7. Study and Site Start and Closure 204
10.1.8. Sponsor's Qualified Medical Personnel 205
10.2. Appendix 2: Clinical Laboratory Tests 206
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 208
10.3.1. Definition of AE 208
10.3.2. Definition of SAE 209
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 211
10.3.4. Reporting of SAEs 214
10.4. Appendix 4: Contraceptive Guidance 215
10.4.1. Male Participant Reproductive Inclusion Criteria 215
10.4.2. Female Participant Reproductive Inclusion Criteria 215
10.4.3. Woman of Childbearing Potential 216
10.4.4. Contraception Methods 217
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 219
10.6. Appendix 6: Abbreviations 221
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 225
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection 228
10.9. Appendix 9: Genetics 229
11. REFERENCES 230

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

LIST OF TABLES

Table 1. Local Reaction Grading Scale 105
Table 2. Systemic Event Grading Scale 105
Table 3. Scale for Fever 106
Table 4. Power Analysis for Noninferiority Assessment 171
Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 173
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility 195
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses 195
Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall 196
Table 9. Laboratory Abnormality Grading Scale 206
Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 226
Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 227

LIST OF FIGURES

Figure 1. Multiplicity Schema 170

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 3 antigens:

BNT162b1 (variant RBP020.3): a modRNA encoding the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5);

BNT162b2 (variant RBP020.2): a modRNA encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9);

BNT162b2s01 (variant RBP020.11): a modRNA encoding the P2 S containing South Africa B.1.351 variant-specific mutations, hereafter referred to as BNT162b2$_{SA}$, as a representative variant of concern (VOC).

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and/or efficacy of these prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	• GMCs/GMTs at the time of Dose 3 and 7 days and 1 month after Dose 3. • GMFRs from before Dose 3 to 7 days and 1 month after Dose 3 • GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2 • GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2.	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof are not approved by the European Medicines Agency

Objectives[a]	Estimands	Endpoints
To describe the safety and tolerability profile of BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants, or as 2 doses to BNT162b2-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2-experienced participants	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 5 or 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary Immunogenicity ***BNT162b2-experienced participants***		
To demonstrate the noninferiority of the anti–reference strain immune response after a third dose of BNT162b2 at 30 µg compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate the noninferiority of the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Objectives[a]	Estimands	Endpoints
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
BNT162b2-experienced participants		
To demonstrate the noninferiority of the anti-SA immune response after a third dose of BNT162b2 at 30 µg compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti–reference strain immune response after 1 dose of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ and a third dose of BNT162b2 at 30 µg	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg	SARS-CoV-2 SA NT in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$ or the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Objectives[a]	Estimands	Endpoints
To descriptively compare the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ and the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate a statistically greater anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 SA NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
To descriptively compare the anti–reference strain immune response after 2 doses of BNT162b2$_{SA}$ and after 2 doses of BNT162b2	GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization	In participants who received BNT162b2 at initial randomization: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate and characterize the SARS-CoV-2 isolate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers • Identification of SARS-CoV-2 variant(s)
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers
To describe the immune response to any VOCs not already specified	Geometric mean NT for any VOCs not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2	• SARS-CoV-2 NTs for any VOCs not already specified
To describe the immune response to a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$	• GMTs at Dose 3 and subsequent time points • GMFRs from Dose 3 to subsequent time points	• SARS-CoV-2 reference strain NTs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and SA in a subset of participants: • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 2 doses to BNT162b2-naïve participants • 7 Days and 1 and 6 months after BNT162b2 given as a third dose to BNT162b2-experienced participants		

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for a description of the manufacturing process.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype $BNT162b2_{VOC}$ at 30 µg (based upon the South African variant and hereafter referred to as $BNT162b2_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive $BNT162b2_{SA}$ given as a 2-dose series, separated by 21 days.

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof in the European Union

For evaluation of boostability and protection against emerging VOCs, 600 existing Phase 3 participants 18 to 55 years of age will be rerandomized in a 1:1 ratio to receive either a third dose of BNT162b2 at 30 µg or a third dose of BNT162b2$_{SA}$.

An additional group of 30 existing Phase 3 participants 18 to 55 years of age will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$. For these 30 participants, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the investigator and sponsor will not be. Serum samples from these participants may be used for assay development purposes and, except for objectives relating to response to a fourth dose, their results will be analyzed separately from the main immunogenicity analyses.

A further group of approximately 144 existing Phase 3 participants 18 years of age and older will be enrolled to receive a third, lower, dose of BNT162b2 of either 5 or 10 µg. Approximately 24 participants 18 to 55 years of age and 48 participants >55 years of age will be enrolled in each dose group.

Three hundred participants 18 to 55 years of age who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19 will be enrolled as a new cohort of participants to receive BNT162b2$_{SA}$ given as a 2-dose series.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 5 µg, 10 µg, 20 µg, 30 µg
- BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S containing South Africa B.1.351 variant–specific mutations): 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated. VE will be demonstrated if the lower bound of the 95% CI for VE is >20%.

In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

The boostability and protection against emerging VOCs for BNT162b2-experienced participants and BNT162b2-naïve participants will be assessed based on GMRs of SARS-CoV-2 SA-neutralizing and/or reference strain–neutralizing titers using a 2-fold noninferiority margin and the difference in percentages of participants with seroresponse using a 10% noninferiority margin.

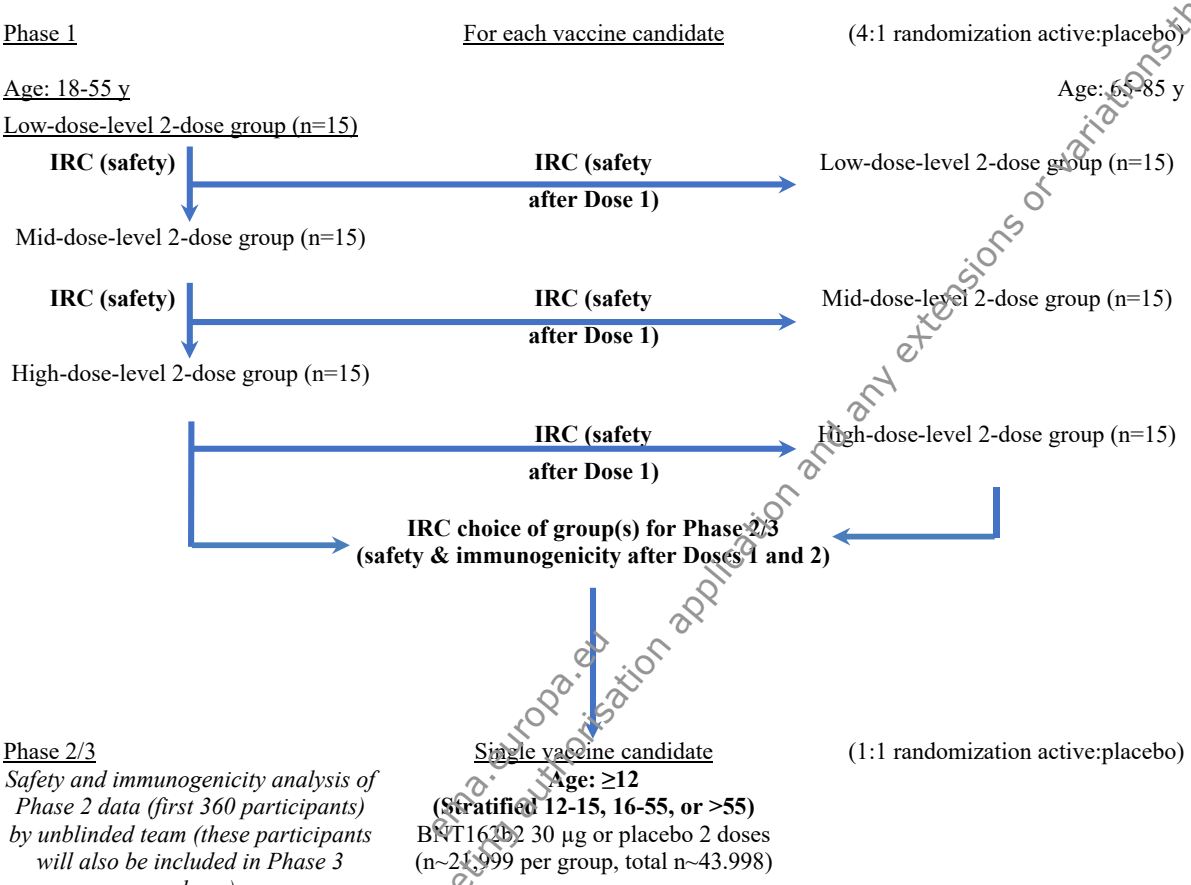
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

Except for the objectives to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age and evaluation of boostability and protection against emerging VOCs by BNT162b2 and BNT162b2$_{SA}$ in Phase 3, the other immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMR, and the associated 95% CIs, for SARS-CoV-2 neutralizing titers, full-length S-binding or S1-binding IgG levels, and/or RBD-binding IgG levels (Phase 1 only) at the various time points.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

1.2. Schema



Abbreviation: IRC = internal review committee.

Note: Participants who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

1.3. Schedule of Activities

The SoA tables provide an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b1 or BNT162b2 (at any dose level) will continue in the study as originally planned.

All other participants will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study no later than at the approximate time participants in Phase 2/3 reach Visit 4. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X								*Continued on table below*		
Assign participant number	X										
Obtain demography and medical history data	X										
Obtain details of medications currently taken	X										
Perform physical examination	X	X	X	X	X	X	X				
Measure vital signs (including body temperature)	X	X	X	X	X	X	X				
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL					
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL										
Serological test for prior COVID-19 infection	~20 mL										
Perform urine pregnancy test (if appropriate)	X	X			X						
Obtain nasal (midturbinate) swab(s)[c]		X			X					X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X			
Confirm eligibility	X	X			X						
Collect prohibited medication use			X	X	X	X	X	X		X	X

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Review hematology and chemistry results		X		X	X	X	X		*Continued on table below*		
Review temporary delay criteria		X			X						
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X			
Obtain randomization number and study intervention allocation		X									
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL			~20 mL
Administer study intervention		X			X						
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X									
Provide thermometer and measuring device		X			X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►		◄	———	►			

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X		*Continued on table below*		
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X		X	X
Collect e-diary or assist the participant to delete application											
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)										X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg **Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9**			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**			
Obtain informed consent		X						
Confirm participant originally received 10 to 30 µg of BNT162b1 or BNT162b2		X						
Perform urine pregnancy test (if appropriate)		X						
Confirm use of contraceptives (if appropriate)		X	X	X				
Collect prohibited medication use	X	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X				
Measure body temperature		X						
Confirm eligibility		X						
Review temporary delay criteria		X						
Collect blood sample for immunogenicity assessment	~20 mL	~20 mL	~20 mL	~20 mL	~20 mL	~20 mL		~20 mL

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg **Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9**			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**			
Obtain nasal (midturbinate) swab(s)		X					X	
Obtain the participant's vaccine vial allocation using the IRT system		X						
Administer 30-µg dose of BNT162b2		X						
Assess acute reactions for at least 30 minutes after study intervention administration		X						
Provide thermometer and measuring device		X						
Remind participant of e-diary technologies		X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		←	→					

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg **Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9**			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**			
Review ongoing reactogenicity e-diary symptoms and obtain stop dates				X				
Collect AEs and SAEs as appropriate	X	X	X	X	X[b]	X[b]	X	X
Collect e-diary or assist the participant to delete application						X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: IRT = interactive response technology; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

This document cannot be used to support any marketing authorisation applications and any extensions or variations thereof ema.europa.eu

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b2 or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b2 will continue in the study as originally planned.

All other participants who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4). If they want to receive BNT162b2, they will be unblinded and those who did originally receive placebo will move to the SoA in Section 1.3.3 for their remaining visits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	Vaccination 1	Vaccination 2	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit[a]	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Day 1[b]	19 to 23 Days After Visit 1	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	350 to 378 Days After Visit 2	714 to 742 Days After Visit 2	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X		
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL		~20 mL/ ~10 mL
Obtain nasal (midturbinate) swab	X	X					X	
Obtain randomization number and study intervention allocation	X							
Administer study intervention	X	X						

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	◄►	◄►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X	X[f]
According to eligibility, ascertain willingness to receive BNT162b2 if originally received placebo; if willing, unblind the participant's study intervention assignment (if not already done), and move placebo recipients to the SoA in Section 1.3.3			X ◄►	X				
Collect e-diary or assist the participant to delete application						X		

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. Any placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2.

Visit Number	101	102	103	104	105	Unplanned	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm participant meets local/national recommending criteria or is at least 175 days after Vaccination 2 (Visit 4/Visit 2)	X						
Obtain informed consent	X						
Confirm participant originally received placebo	X						
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X					
Collect prohibited medication use	X	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X		
Review and consider eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment	~20 mL						~20 mL
Obtain nasal (midturbinate) swab	X	X				X	
Obtain vaccine vial allocation via IRT	X	X					
Administer BNT162b2	X	X					

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Visit Number	101	102	103	104	105	Unplanned	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Collect AEs and SAEs as appropriate	X	X	X	X		X[d]	X[d]
Contact the participant by telephone			X	X	X		
Request the participant return the e-diary or assist the participant to delete the application					X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)						X	X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

a. For participants who become eligible according to recommendations detailed separately and available in the electronic study reference portal.
b. For any remaining Phase 2/3 placebo recipients who wish to receive BNT162b2; may be combined with Visit 4 for Phase 2/3 participants.
c. Only if the participant has no blood sample collected in the previous 7 days.
d. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.4. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg)

Select participants in Phase 3 at select sites who originally received 2 doses of BNT162b2 will be offered the opportunity to receive a third (and potentially fourth) dose of BNT162b2 or BNT162b2$_{SA}$.

Visit Number	301	302	303	304	305	306	307	Unplanned	Unplanned
Visit Description	Vax 3[a]	1-Week Follow-up Visit (After Vax 3)	1-Month Follow-up Visit (After Vax 3)	1-Week Follow-up Visit (After Vax 4)[b]	1-Month Follow-up Visit (After Vax 4)[b]	6-Month Follow-up Visit	18-Month Follow-up Visit	Potential COVID-19 Illness Visit[c]	Potential COVID-19 Convalescent Visit
Visit Window (Days)	150 to 210 Days After Visit 2	6 to 8 Days After Visit 301	28 to 35 Days After Visit 301	6 to 8 Days After Visit 303	28 to 35 Days After Visit 303	175 to 189 Days After Visit 301	532 to 560 Days After Visit 301	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4					
Obtain informed consent	X								
Confirm participant originally received BNT162b2 at Dose 1 and Dose 2	X								
Perform urine pregnancy test (if appropriate)	X		X[b]						
Confirm use of contraceptives (if appropriate)	X	X	X	X	X				
Collect prohibited medication use	X	X	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X	X	X			
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X			X	X		
Measure body temperature	X		X[b]						
Confirm eligibility	X		X[b]						

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Visit Number	301	302	303	304	305	306	307	Unplanned	Unplanned
Visit Description	**Vax 3[a]**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**1-Week Follow-up Visit (After Vax 4)[b]**	**1-Month Follow-up Visit (After Vax 4)[b]**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[c]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**150 to 210 Days After Visit 2**	**6 to 8 Days After Visit 301**	**28 to 35 Days After Visit 301**	**6 to 8 Days After Visit 303**	**28 to 35 Days After Visit 303**	**175 to 189 Days After Visit 301**	**532 to 560 Days After Visit 301**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			**ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4**					
Review temporary delay criteria	X		X[b]						
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL		~20 mL
Collect blood sample for PBMC isolation[d]	~120 mL	~120 mL	~120 mL			~120 mL			
Collect blood sample for HLA typing[d]	~5 mL								
Obtain nasal (midturbinate) swab(s)	X		X[b]					X	
Obtain randomization number and study intervention allocation using the IRT system	X								
Administer study intervention	X		X[b]						
Assess acute reactions for at least 30 minutes after study intervention administration	X		X[b]						
Provide thermometer and measuring device	X								
Remind participant of e-diary technologies	X		X[b]						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	◄	———	►	◄	►				

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document can be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	301	302	303	304	305	306	307	Unplanned	Unplanned
Visit Description	**Vax 3[a]**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**1-Week Follow-up Visit (After Vax 4)[b]**	**1-Month Follow-up Visit (After Vax 4)[b]**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[c]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**150 to 210 Days After Visit 2**	**6 to 8 Days After Visit 301**	**28 to 35 Days After Visit 301**	**6 to 8 Days After Visit 303**	**28 to 35 Days After Visit 303**	**175 to 189 Days After Visit 301**	**532 to 560 Days After Visit 301**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			**ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4**					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates			X		X				
Collect AEs and SAEs as appropriate	X	X	X	X	X	X[e]	X[e]	X	X[e]
Collect e-diary or assist the participant to delete application							X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)								X	X

Abbreviations: e-diary = electronic diary; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; vax = vaccination.

a. Visit 301 can occur on the same day as Visit 4, but all procedures for both visits must be conducted (including collection of all blood samples).
b. Only for those participants who will receive Dose 4.
c. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
d. Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants who will receive a third (but not fourth) dose of BNT162b2 at 30 µg or BNT162b2$_{SA}$ at select sites only.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.5. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants

As part of Amendment 14, an additional cohort of BNT162b2-naïve participants will be enrolled to receive BNT162b2$_{SA}$ per the following SoA.

Visit Number	401	402	403	404	405	406	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X	X				
Collect nonstudy vaccine information	X	X	X	X	X			
Collect prohibited medication use		X	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X			X	X	X		
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment	~50 mL		~50 mL	~50 mL	~50 mL	~50 mL		~20 mL
Collect blood sample for PBMC isolation[d]	~120 mL		~120 mL	~120 mL	~120 mL			
Collect blood sample for HLA typing[d]	~5 mL							

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Visit Number	401	402	403	404	405	406	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain nasal (midturbinate) swab	X	X					X	
Obtain the participant's vaccine vial allocation using the IRT system	X	X						
Administer BNT162b2$_{SA}$	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	◄►	◄►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X		X				
Collect AEs and SAEs as appropriate	X	X	X	X	X[e]	X[e]	X	X[e]
Collect e-diary or assist the participant to delete application						X		

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Visit Number	401	402	403	404	405	406	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: e-diary = electronic diary; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; vax = vaccination.

a. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
b. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
c. Including, if indicated, a physical examination.
d. Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants at select sites only.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

1.3.6. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4 or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

Visit Number	201	202 Onward
Visit Description	**Asymptomatic SARS-CoV-2 Infection Surveillance Consent**	**Asymptomatic SARS-CoV-2 Infection Surveillance Swab**
Visit Window (Days)	**From Approval of Protocol Amendment 11**	**Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection**
Obtain informed consent for asymptomatic SARS-CoV-2 infection surveillance	X	
Collect prohibited medication use	X	
Collect blood sample for immunogenicity assessment[a]	~20 mL/~10 mL	
Obtain nasal (midturbinate) swab (self-swab at home or by site staff at an in-person visit)	X	X
Collect AEs and SAEs as appropriate[b]	X	

a. Only if the participant has no blood sample collected in the previous 7 days. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
b. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no licensed vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

As more data about COVID-19 continue to accrue, the potential duration of protection afforded after a wild-type SARS-CoV-2 infection, and by vaccination, remains unknown. In addition, mutated SARS-CoV-2 VOCs have started to emerge, for example in the UK (known as 20I/501Y.V1, VOC 202012/01, or B.1.1.7), SA (known as 20H/501Y.V2 or B.1.351), and Brazil (known as P.1).[4]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[5,6]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may

be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Three SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 3 antigens:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5);

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9);

- **BNT162b2s01** (variant RBP020.11): nucleoside-modified messenger RNA (modRNA) as above, but encoding the P2 S containing South Africa B.1.351 variant–specific mutations, hereafter referred to as BNT162b2$_{SA}$, as a representative variant of concern (VOC).

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

In light of the unknowns regarding duration of protection, as well as the emerging VOCs, it is important to understand the boostability of BNT162, and potential heterologous protection against emerging VOC(s). A first step to address this will be to study an additional dose of BNT162b2 at 30 µg given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ (based upon the South African variant and hereafter referred to as BNT162b2$_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

This document can only be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[7] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[8] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with the currently available therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.

- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.

- All participants 12 to 15 years of age will be included in the reactogenicity subset (see Section 8.2.2).

This document cannot be used to support a marketing authorisation application or any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[9]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of an efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	• GMCs/GMTs at the time of Dose 3 and 7 days and 1 month after Dose 3. • GMFRs from before Dose 3 to 7 days and 1 month after Dose 3	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels
	• GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers
	• GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Objectives	Estimands	Endpoints
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Objectives[a]	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants, or as 2 doses to BNT162b2-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2-experienced participants	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 5 or 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary Immunogenicity ***BNT162b2-experienced participants***		
To demonstrate the noninferiority of the anti–reference strain immune response after a third dose of BNT162b2 at 30 µg compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Objectives[a]	Estimands	Endpoints
BNT162b2-naïve participants		
To demonstrate the noninferiority of the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
BNT162b2-experienced participants		
To demonstrate the noninferiority of the anti-SA immune response after a third dose of BNT162b2 at 30 µg compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Objectives[a]	Estimands	Endpoints
To demonstrate the noninferiority of the anti–reference strain immune response after 1 dose of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ and a third dose of BNT162b2 at 30 µg	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg	SARS-CoV-2 SA NT in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$ or the third dose of BNT162b2 at 30 µg) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ and the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate a statistically greater anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 SA NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
To descriptively compare the anti–reference strain immune response after 2 doses of BNT162b2$_{SA}$ and after 2 doses of BNT162b2	GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Objectives[a]	Estimands	Endpoints
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization	In participants who received BNT162b2 at initial randomization: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate and characterize the SARS-CoV-2 isolate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers • Identification of SARS-CoV-2 variant(s)
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers
To describe the immune response to any VOCs not already specified	Geometric mean NT for any VOCs not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2	• SARS-CoV-2 NTs for any VOCs not already specified
To describe the immune response to a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$	• GMTs at Dose 3 and subsequent time points • GMFRs from Dose 3 to subsequent time points	• SARS-CoV-2 reference strain NTs
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and SA in a subset of participants: • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 2 doses to BNT162b2-naïve participants • 7 Days and 1 and 6 months after BNT162b2 given as a third dose to BNT162b2-experienced participants		

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for description of the manufacturing process.

Up until the final efficacy analysis, this protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ at 30 µg (based upon the South African variant and hereafter referred to as

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

BNT162b2$_{SA}$). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than at the approximate time participants in Phase 2/3 reach Visit 4.

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162.

Participants are expected to participate for up to a maximum of approximately 26 months.

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 280 participants from each of the 2 age groups (12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

For evaluation of boostability and protection against emerging VOCs, 600 existing Phase 3 participants 18 to 55 years of age will be rerandomized in a 1:1 ratio to receive either a third dose of BNT162b2 at 30 µg or a third dose of BNT162b2$_{SA}$.

A further group of approximately 144 existing Phase 3 participants 18 years of age and older will be enrolled to receive a third, lower, dose of BNT162b2 of either 5 or 10 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Approximately 24 participants 18 to 55 years of age and 48 participants >55 years of age will be enrolled in each dose group. An additional group of 30 existing Phase 3 participants 18 to 55 years of age will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$. For these 30 participants, through 1 month after their first dose of BNT162b2$_{SA}$ the participant will be blinded to their vaccine allocation but the investigator and Sponsor will not be. Serum samples from these participants may be used for assay development purposes and, except for objectives relating to response to a fourth dose, their results will be analyzed separately from the main immunogenicity analyses.

Three hundred participants 18 to 55 years of age who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19 will be enrolled as a new cohort of participants to receive BNT162b2$_{SA}$ given as a 2-dose series.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 2/3 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4).

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

The changes to the protocol as part of protocol amendment 14 to assess boostability and homologous/heterologous protection against emerging VOCs allow the evaluation of safety and immunogenicity of BNT162b2$_{SA}$:

- When given as a third dose to C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously (ie, BNT162b2-experienced) and have not experienced COVID-19.
- In a small separate group of individuals who previously received 2 doses of BNT162b2 followed by 1 dose of BNT162b2$_{SA}$, a second BNT162b2$_{SA}$ dose will also be given 1 month after Dose 1 of BNT162b2$_{SA}$.
- When given as a 2-dose series, separated by 21 days, in newly recruited participants who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

In addition, a group of C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously will receive a third dose of BNT162b2.

This approach will allow an evaluation of immunogenicity against the reference ancestral SARS-CoV-2 strain (Wuhan-Hu-1/USA-WA1) and the selected South African VOC, using a noninferiority approach based on neutralizing antibody titers in prior BNT162b2 vaccinees who receive either a homologous boost (with BNT162b2) or a heterologous boost (with BNT162b2$_{SA}$), as well as new vaccinees receiving 2 doses of BNT162b2$_{SA}$.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.6. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization.

   For the boostability and protection-against-VOCs subset:

   - Existing participants enrolled to receive a third dose of BNT162b2 at 30 µg or BNT162b2$_{SA}$; male or female participants between the ages of 18 and 55 years, inclusive, at rerandomization.
   - Newly enrolled participants enrolled to receive 2 doses of BNT162b2$_{SA}$; male or female participants between the ages of 18 and 55 years, inclusive, at enrollment.
   - Existing participants enrolled to receive a third dose of BNT162b2 at 5 or 10 µg; male or female participants ≥18 years at rerandomization.

   Note that participants <18 years of age cannot be enrolled in the EU.

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during

the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

5. **Boostability and protection-against-VOCs existing participant subset only:** Participants who provided a serum sample at Visit 3, with Visit 3 occurring within the protocol-specified window.

Informed Consent:

6. Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Chronic pulmonary disease
- Asthma
- Current vaping or smoking
- History of chronic smoking within the prior year
- Chronic liver disease
- Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
- Resident in a long-term facility
- BMI >30 kg/m^2
- Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry through and including 6 months after the last dose of study intervention, with the exception of interventional studies for prevention of COVID-19, which are prohibited throughout study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Sore throat;
- Diarrhea;
- Vomiting.

2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.

3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 3 investigational RNA vaccine candidates, with the addition of saline placebo, are the 4 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 5 µg, 10 µg, 20 µg, 30 µg
- BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S containing South Africa B.1351 variant–specific mutations): 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	5-, 10-, 20-, 30-µg	30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. Participants who originally received placebo and accept the offer to receive BNT162b2 at defined points as part of the study will receive 1 dose of BNT162b2 at each additional vaccination visit (Visits 101 and 102) in accordance with the study's additional SoA (Section 1.3.3). The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162 at Visit 8a.

Participants in the subset for evaluation of boostability and protection against emerging VOCs will receive either a third dose of BNT162b2 or BNT162b2$_{SA}$ approximately 5 to 7 months after their second dose of BNT162 at Visit 301. Of those who receive BNT16b2$_{SA}$ at Visit 301, a subset will receive a further dose of BNT162b2$_{SA}$ at Visit 303.

BNT162b2-naïve participants who are enrolled under protocol amendment 14 to receive BNT162b2$_{SA}$ will receive 1 dose of study intervention at each vaccination visit, Visits 401 and 402.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

9. Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

To allow administration of BNT162b2 to participants who originally received placebo, site staff will be unblinded to individual participants' original study intervention allocation as the participants become eligible for vaccination under local/national recommendations or from 6 months after the second dose.

For the group of 30 existing Phase 3 participants 18 to 55 years of age who will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the investigator will not be.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).

- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.

- An unblinded team supporting interactions with and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

- After the formal data release of the final efficacy analysis of at least 164 cases, which is considered the primary completion of the study efficacy objectives, additional statisticians and programmers will become unblinded at the participant level to prepare unblinded analyses and other regulatory activities. A group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study.

- After the study data used for submission become public, the blinded study team will also have access to those data, and become unblinded at a group level.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- When a participant is unblinded for potential receipt of BNT162b2 (if he or she originally received placebo) per Section 8.16, the study team will become unblinded to the participant's original study intervention allocation.

For the group of 30 existing Phase 3 participants 18 to 55 years of age who will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the sponsor will not be.

The study will be unblinded in stages once all ongoing participants either have been individually unblinded or have concluded their 6-month post–Dose 2 study visit, as follows:

- Phase 1 (after Visit 8).
- Phase 2/3, ≥16 years (after Visit 4).
- Phase 3, 12 to 15 years (after Visit 4).
- Original Phase 3 participants rerandomized to assess boostability and protection against emerging VOCs (after Visit 306).

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

Instructions on how to unblind participants ahead of administration of BNT162b2 to placebo recipients, or for other, nonemergency reasons, will be provided separately: this unblinding will NOT be performed in the IRT. The date (that the participant becomes aware of study intervention allocation) and reason that the blind was broken must be recorded in the source documentation and CRF.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants). In addition, for Phase 1 participants who go on to receive a third dose of BNT162, concomitant vaccinations will be collected from the time the participant provides informed consent (for receipt of Vaccination 3) through and including Visit 8c (1 month after the third dose). For BNT162-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to the time the participant provides informed consent (for participation in the subset) through and including Visit 306. For BNT162b2-naïve participants, the subset for evaluation of protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to study enrollment through and including Visit 405.

- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 and from 28 days prior to Visit 8a to Visit 8c for Phase 1 participants, and from 28 days prior to enrollment to Visit 3 for Phase 2/3 participants). Use is also prohibited for participants in the subset for evaluation of

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

boostability and protection against emerging VOCs, from 28 days prior to Visit 301 to Visit 303/305 and the BNT162b2-naïve participants from 28 days prior to enrollment to Visit 404.

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 2 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, for whatever reason, a participant receives only 1 dose of BNT162b2, the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. For example, because of a medication error a participant receives only 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa); the participant can return at a later date for the unscheduled visit. In this situation:

- Obtain informed consent.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Discuss contraceptive use as described in Section 10.4.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s).

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

If a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately up to: 500 mL for participants in Phase 1, 110 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum.

Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 670 mL during the 24-month study period.

For those Phase 3 participants enrolled in the subset to receive an additional dose of BNT162b2 or BNT162b2$_{SA}$, the total blood sampling volume for individual participants in this study is approximately up to 310 mL for those who receive 3 doses and 410 mL for those who receive 4 doses. Those participants in the subset who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of approximately up to 795 mL.

For those participants enrolled into the additional cohort (added as part of protocol amendment 14) of BNT162b2-naïve participants who will receive 2 doses of BNT162b2$_{SA}$, the total blood sampling volume for individual participants is approximately up to 250 mL.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emea.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Those participants in the cohort who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of approximately up to 735 mL.

Additionally, 20 mL of blood for participants ≥16 years of age and 10 mL for participants in the 12- to 15-year age stratum will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection.

For all participants, other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

8.1.1. Efficacy Against COVID-19

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[10] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
  - Fever;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction*;
  - Admission to an ICU;
  - Death.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu/
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

The DMC may recommend modification of the definition of severe disease according to emerging information.

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

8.1.2. Efficacy Against Asymptomatic SARS-CoV-2 Infection

VE against asymptomatic SARS-CoV-2 infection will be evaluated in 2 ways, through impact on seroconversion of N-binding antibody and impact on NAAT-confirmed SARS-CoV-2 infection, in originally enrolled Phase 2/3 participants not suffering from COVID-19. Data from participants who receive more than 2 doses of BNT162b2 will not be included after they receive a third dose.

8.1.2.1. Seroconversion of N-Binding Antibody

Blood samples for assessment of N-binding antibodies are drawn at multiple scheduled visits. An asymptomatic case of SARS-CoV-2 infection based on seroconversion of N-binding antibody is defined as positive N-binding antibody at a post–Dose 2 visit in participants without serological evidence of infection (determined by negative N-binding antibody) at Visit 1 or virological evidence of infection (determined by negative NAAT result at Visit 1 and Visit 2 and at the time of a potential COVID-19 illness). The requirement for a negative NAAT result at Visit 2 is to focus on assessment of protection against asymptomatic infection after 2 doses of vaccine, to the extent possible in an analysis based on seroconversion of N-binding antibody, recognizing that it is not possible to identify and exclude all asymptomatic infections that occur after Dose 1 and prior to Dose 2.

A secondary definition will be applied without the requirement for a negative NAAT result at Visit 2 to allow assessment of protection after 1 dose of vaccine. A positive N-binding antibody at a postvaccination visit in participants with negative N-binding antibody at Visit 1 and negative NAAT results at Visit 1 and at the time of a potential COVID-19 illness is considered an asymptomatic case.

8.1.2.2. NAAT-Confirmed SARS-CoV-2 Infection

For participants who consent to participate in an intensive period of surveillance, nasal swabs will be obtained to assess SARS-CoV-2 infection by NAAT (see Section 8.1.5).

An asymptomatic case of NAAT-confirmed SARS-CoV-2 infection is defined as a positive NAAT result on a nasal swab collected during the surveillance period from participants without COVID-19 symptoms at the time the nasal swab was taken, or within 14 days after it. The onset date of the asymptomatic case is the collection date of the first nasal swab that tested positive.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.1.3. Vaccine-Induced Immunogenicity

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay (reference strain and SA variant)
- Full-length S-binding or S1-binding IgG level assay
- RBD-binding IgG level assay (Phase 1 only)

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

Additional whole blood samples of ~120 mL will be obtained from a group of up to approximately 30 participants in each 30-µg group in the subset for evaluation of boostability and protection against emerging VOCs (both BNT162b2-experienced and BNT162b2-naïve) at select sites for isolation of PBMCs. These samples will be used to describe T-cell responses to emerging VOCs and reference strains. Some of the sample may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs, for understanding the B-cell, T-cell, and antibody repertoires. A blood sample of ~5 mL for HLA typing will also be obtained. Some of the 5-mL blood sample collected for HLA typing may be used for DNA and/or RNA isolation to further characterize HLA type.

8.1.4. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine related assay work supporting vaccine programs. No testing of the participant's DNA will be performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

confidentiality is maintained and no testing of the participant's DNA is performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

8.1.5. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.6.

The nasal swabs will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2. For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with Section 8.3.2.

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Certain participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. In addition, participants 16 through 17 years of age enrolled under protocol amendment 9 and onwards will be included in the reactogenicity subset. All other participants, including those who originally received placebo and then received BNT162b2 under protocol amendment 10 and onwards, will not complete a reactogenicity e-diary but will have their local reactions and systemic events detected and reported as AEs in accordance with Section 8.3.2. Phase 1 participants who receive a third dose of BNT162b2 will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage in the reactogenicity e-diary for 7 days following administration of the study intervention. Participants in the subset for evaluation of boostability and protection against emerging VOCs (both BNT162b2-experienced and BNT162b2-naïve) will be asked to monitor and record local reactions, systemic events, and antipyretic medication use in the reactogenicity e-diary for 7 days following each administration of the study intervention.

The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[9]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the administration of the second dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

Administration of BNT162b2 at Visits 101 and 102 to pregnant participants who originally received placebo and choose to be unblinded and receive BNT162b2 may be considered if there are local or national recommendations for COVID-19 vaccination of pregnant women, and the investigator and participant are in agreement. This overrides the requirements stated in the previous paragraph, and will not be considered as a protocol deviation. However, the EDP should still be reported in accordance with Section 8.3.5.1.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Additionally, for those participants who originally received placebo but go on to receive BNT162b2 at Vaccinations 3 and 4, AEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) through and including Visit 103. SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) to approximately 6 months after the second dose of BNT162b2 (Visit 104).

For Phase 1 participants who go on to receive a third dose of BNT162, AEs and SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccination 3) through and including Visit 8c (1 month after the third dose).

For BNT162b2-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, AEs will be collected from the time the participant provides informed consent (for participation in the subset) through and including Visit 303 for those receiving 1 additional dose and Visit 305 for those who receive 2 additional doses. For both schedules, this equates to collection for up to 1 month after the last dose. SAEs will be collected from the time the participant provides informed consent (for participation in the subset) through and including Visit 306 (5 or 6 months after the last dose, depending upon group).

For BNT162b2-naïve participants, the subset for evaluation of protection against emerging VOCs, AEs will be collected from the time the participant provides informed consent through and including Visit 404 (1 month after the second dose). SAEs will be collected from the time the participant provides informed consent through and including Visit 405 (6 months after the second dose).

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:

  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.

  - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose of study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.6. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.6.1. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

8.3.7. Cardiovascular and Death Events

Not applicable.

8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.9. Adverse Events of Special Interest

Not applicable.

8.3.9.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.3.10. Medical Device Deficiencies

Not applicable.

8.3.11. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Some of the blood samples collected for PBMC isolation and HLA typing may be used for DNA and/or RNA isolation. The DNA and/or RNA samples from the PBMC isolation may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs, for understanding the B-cell, T-cell, and antibody repertoires. The DNA and/or RNA samples from the blood sample for HLA typing may be used to further characterize HLA type.

See Appendix 9 for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

Unless stated otherwise, all study visits are intended to be conducted in person at the study site. If this is not possible, because of local circumstances related to the COVID-19 pandemic, study procedures that do not require in-person participant contact may be performed by telehealth. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Irrespective of the nature of the contact, all visit procedures are expected to be performed on the same day.

As the protocol design includes visits of an unplanned nature, multiple visits may occur on the same day, but all procedures for all visits must be conducted (including collection of all blood samples).

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
the european
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 100 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Between Visits 8 and 9

All participants who have not already been unblinded, no later than at the approximate time participants in Phase 2/3 reach Visit 4, will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, he or she will move to the procedures in Section 8.16.

8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of a third dose of BNT162, his or her next visit should be Visit 9.

- Confirm that the participant originally received 10-µg, 20-µg, or 30-µg doses of BNT162b1 or BNT162b2 at Vaccinations 1 and 2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Record nonstudy vaccinations as described in Section 6.5.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 2, 3, and 6 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer a 30-µg dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
    - Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
    - Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):
        - Fever ≥39.0°C (≥102.1°F)
        - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)
        - Severe pain at the injection site
        - Any severe systemic event
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.

- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
    - Severe pain at the injection site.
    - Any severe systemic event.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.

- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- If Visit 3 is being conducted under amendment 12 onward: If the participant is eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, determine if he/she is willing to receive BNT162b2 as part of the study. If so, unblind the participant's study intervention assignment, and move placebo recipients to the procedures in Section 8.16.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- If not already unblinded, unblind the participant's study intervention assignment, and move placebo recipients willing to receive BNT162b2 to the procedures in Section 8.16.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;

- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;

- Fever;

- New or increased cough;

- New or increased shortness of breath;

- Chills;

- New or increased muscle pain;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
  - Symptoms and signs, including
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
    - Significant acute renal, hepatic, or neurologic dysfunction

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

  - Clinical diagnosis
  - Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.
  - Full blood count
  - Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
  - Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
  - Number and type of any healthcare contact; duration of hospitalization and ICU stay
  - Death
- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

8.15. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 or 14 days after receipt of the second dose, depending on the objective) of past SARS-CoV-2 infection.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

- Asymptomatic SARS-CoV-2 infection surveillance visits: To determine the incidence of asymptomatic SARS-CoV-2 infection.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, asymptomatic SARS-CoV-2 infection surveillance visit swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result, either asymptomatic or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result), prior to Visit 2 should receive Vaccination 2 as normal.

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

If a participant becomes eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study.

Placebo recipients who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Dose 2, and will follow the procedures listed in this section for the remainder of their participation in the study. For Phase 2/3 participants, Visit 101 could occur at the same time as the original Visit 4.

8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant originally received only placebo at Vaccination 1/2. Secondary confirmation by another site staff member is required.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 4 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101)

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Record AEs as described in Section 8.3.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record AEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 103 (if any).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment to call the participant by telephone for the next study contact.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 104 (if any).

- Request the return of the participant's e-diary or assist the participant/participant's parent(s)/legal guardian to remove the study application from his or her own personal device.

- Inform the participant/participant's parent(s)/legal guardian that his or her study participation has ended.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.17. Administration of an Additional Dose of BNT162b2 (5, 10, or 30 µg) or BNT162b2$_{SA}$ (30 µg)

The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 or a third and potentially a fourth dose of prototype BNT162b2$_{SA}$.

8.17.1. Visit 301 – Vaccination 3: (150 to 210 Days After Visit 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of a third dose of BNT162b2, he or should remain on the Phase 2/3 visit schedule.

Note: This visit can occur on the same day as Visit 4, but all procedures for both visits must be conducted (including collection of all blood samples).

- Confirm that the participant originally received BNT162b2 at Vaccinations 1 and 2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Record nonstudy vaccinations as described in Section 6.5.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 1, 2, 3, 5, and 6 are met and exclusion criteria 1, 3, 5, 8, 10, 11, 12, 13, 15, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. **The IRT system will also assign an additional single participant number; this number will not be used as the primary identifier for the participant, but must be included in the participant's source documents and transcribed into the CRF**. The system will also identify those participants who are to

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

receive a fourth dose; this should be kept blinded until from the participant until Visit 303.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

    - Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

    - Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):

        - Fever ≥39.0°C (≥102.1°F)

        - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)

        - Severe pain at the injection site

        - Any severe systemic event

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.17.2. Visit 302 – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 301)

- Record AEs as described in Section 8.3.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Discuss contraceptive use as described in Section 10.4.

- Collect a blood sample of approximately 50 mL for immunogenicity testing.

- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.17.3. Visit 303 – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 301)

- Record AEs as described in Section 8.3.

- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.

Only if the participant is to receive a further dose of BNT162b2$_{SA}$:

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 1, 2, 3, 5, and 6 are met and exclusion criteria 1, 3, 5, 8, 10, 11, 12, 13, 15, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Fever ≥39.0°C (≥102.1°F)
- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)
- Severe pain at the injection site
- Any severe systemic event

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.4. Visit 304 – 1-Week Follow-up Visit (Vaccination 4): (6 to 8 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2SA

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- The investigator or an authorized designee completes the CRFs.

8.17.5. Visit 305 – 1-Month Follow-up Visit (Vaccination 4): (28 to 35 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.6. Visit 306 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 301):

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- For participants who are HIV-positive, record latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.17.7. Visit 307 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 301):

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record latest CD4 count and HIV viral load.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.18. Administration of BNT162b2$_{SA}$ to BNT162b2-naïve Participants

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

8.18.1. Visit 401 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - Provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (≥20 measuring device units).
    - Severe pain at the injection site.
    - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the study intervention accountability records.

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.18.2. Visit 402 – Vaccination 2: (19 to 23 Days After Visit 401)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- The investigator or an authorized designee completes the CRFs and the study intervention accountability records.

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.18.3. Visit 403 – 1-Week Follow-up Visit (After Vaccination 2): (6 to 8 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.18.4. Visit 404 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.18.5. Visit 405 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.18.6. Visit 406 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 402)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.19. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11 until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The surveillance will be conducted per the procedures listed below.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.19.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11

Before surveillance begins and any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

The visit should be conducted only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1) and this visit should be temporarily delayed until the symptoms have resolved.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 3 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Record AEs as described in Section 8.3 (only if the participant remains in the AE reporting period; see Section 8.3.1).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Ask the participant to obtain a surveillance self-swab at home in approximately 14 days or schedule an appointment for the participant to return to collect the swab at the site. The swab should be collected only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

8.19.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection

This is a repeating swab collection and will be conducted approximately every 14 days until the intensive surveillance period ends.

- Participant collects a self-swab and ships it to the site for assessment at the central laboratory. The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- Complete the source documents with the swab information.

- The investigator or an authorized designee completes the CRFs with the swab information.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by all-available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either $VE_1 > 30\%$ or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated based on the lower bound of the 95% CI. VE will be demonstrated if the lower bound of the 2-sided 95% CI for VE is >20%.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

9.1.2.2.1. Hypothesis for Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month

This document cannot be used to support any marketing authorisation application and extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

after Dose 2. If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

9.1.2.2.2. Hypotheses for Boostability and Protection Against Emerging SARS-CoV-2 VOCs

The primary and secondary objectives for boostability and protection against emerging VOCs for BNT162b2-experienced participants and BNT162b2-naïve participants will be assessed based on:

- GMRs of SARS-CoV-2 SA and/or reference strain neutralizing titers using a 2-fold noninferiority margin. Noninferiority is met if the lower limit of the alpha adjusted CI for the GMR is >0.5.

- The difference in percentages of participants with seroresponse to SA and/or reference strain using a 10% noninferiority margin. Noninferiority is met if the lower limit of the alpha-adjusted CI for the difference in percentages of participants with seroresponse is >-10%.

Seroresponse is defined as achieving ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

9.1.2.2.2.1. Multiplicity Control for the Boostability and Protection-Against-VOCs Objectives

Figure 1 outlines the type I error control strategy for multiple objectives across different populations (BNT162b2-experienced or BNT162b2-naïve) and estimands (GMR or seroresponse).

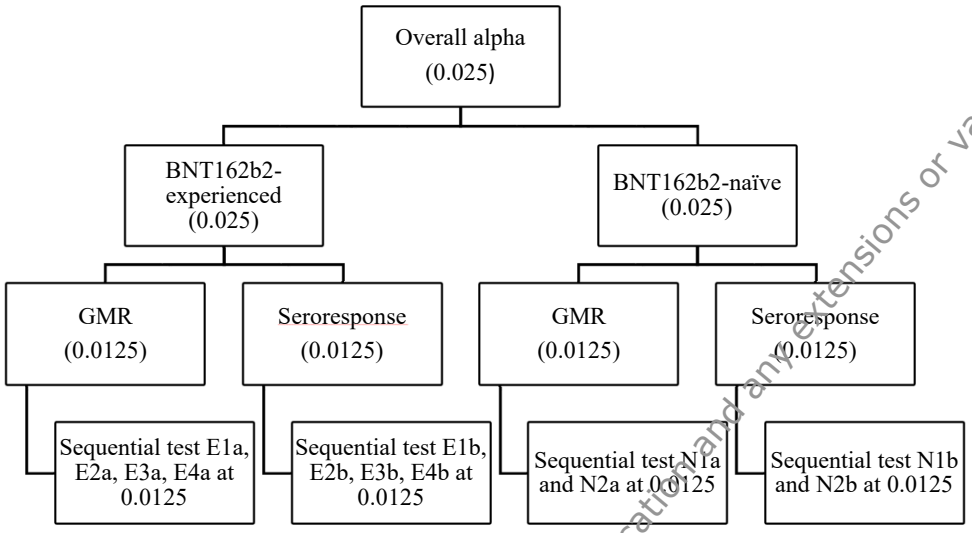
The objectives for BNT162b2-experienced participants and BNT162b2-naïve participants will be evaluated independently. The vaccine-experienced and -naïve individuals are different populations with different objectives. The 2 populations are included in the same study to improve operational efficiency. Therefore, no type I error adjustments will be applied to the assessments of the 2 populations.

For each population, the objectives will be evaluated separately for each estimand. To control the overall type I error, the 1-sided alpha of 0.025 will be split and allocated equally to each estimand. Specifically, for each estimand, the hypotheses will be tested in sequential order (as listed in the objectives in Section 3) using a 1-sided alpha of 0.0125 (Figure 1, where E and N represent vaccine-experienced and vaccine-naïve, respectively, and a and b represent GMR and seroresponse estimands, respectively).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Figure 1. Multiplicity Schema



9.2. Sample Size Determination

9.2.1. Phase 1

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

9.2.2. Efficacy Against COVID-19

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

9.2.3. Efficacy Against Asymptomatic Infection

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection will be assessed in Phase 2/3 participants (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT). Assuming a true VE of 70%, a total of 53 asymptomatic cases will provide approximately 90% power to conclude true VE >20%. A total of 206 cases is needed to have 90% power if the true VE is 50%. The hypothesis for asymptomatic seroconversion of N-binding antibody will be tested if at least 206 cases are accrued. The hypothesis for asymptomatic infection based on central laboratory–confirmed NAAT in participants who are consented to participate in the intensive surveillance phase will be tested if at least 53 cases are accrued.

9.2.4. Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 280 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.65	-0.2	225	90.4%

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer.
a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).
b. At 0.05 alpha level (2-sided).

9.2.5. Boostability and Protection Against Emerging SARS-CoV-2 VOCs

To assess boostability and protection against emerging SARS-CoV-2 VOCs, approximately 300 participants will be enrolled in each of the 3 groups (BNT162b2-experienced participants to receive either a third dose of BNT162b2 at 30 µg [Group 1] or a third dose of BNT162b2$_{SA}$ [Group 2], BNT162b2-naïve participants to receive 2 doses of BNT162b2$_{SA}$ [Group 3]) to provide an acceptable safety database.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Assuming 20% nonevaluable rate, approximately 240 evaluable participants in each group will contribute to immunogenicity evaluation. This will provide sufficient power for noninferiority evaluations with appropriate multiplicity adjustment for type I error control.

For comparisons based on GMR, the assay standard deviation in log scale is assumed to be 0.74 based on results from Phase 2 of the study and adjusted for assay variability. A GMR of 1 is assumed for each comparison.

For comparisons based on seroresponse, a 90% response rate is assumed for each comparative group or at each comparative time point.

Within-Group Comparison for BNT162b2-Experienced Participants

For each randomized group of BNT162b2-experienced participants (Group 1: received a third dose of BNT162b2 at 30 μg and Group 2: received a third dose of $BNT162b2_{SA}$), with 240 evaluable participants and the stated assumptions for the GMR and standard deviation, the study has >99.9% power to demonstrate NI based on GMR for the objectives in vaccine-experienced individuals using a 2-fold margin.

Assuming true response rate of 90% in each group, the study has 89.7% power to show NI based on seroresponse rate for the objectives in vaccine-experienced individuals using a 10% margin.

Between-Group Comparison of BNT162b2-Naïve Participants to Selected Existing Phase 3 Participants Who Received 2 Doses of BNT162b2

Approximately 300 participants will be selected from the existing Phase 3 participants who received 2 doses of BNT162b2 to form the control group for the BNT162b2-naïve participants. The selection will ensure comparable distribution of age, sex, and other demographic factors in the control group and BNT162b2-naïve group. With 240 evaluable BNT162b2-naïve participants and 240 evaluable participants in the control group and the above stated assumptions for the GMR, standard deviation, and seroresponse rate, the study has >99.9%% power to declare NI based on GMR for the objectives in vaccine-naïve individuals using a 2-fold margin and 89.7% power to declare NI based on seroresponse rate using a 10% margin.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

9.2.6. Safety

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=300	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.03	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.06	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.11	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.16	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.21	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.26	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.36	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.45	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.53	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.59	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.65	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.78	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	0.95	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 3 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 as initially randomized, with Dose 2 received within the predefined window, receive a third dose of BNT162b2 or $BNT162b2_{SA}$ as rerandomized, have at least 1 valid and determinate immunogenicity result after Dose 3 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 4 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 as initially randomized, with Dose 2 received within the predefined window, receive 2 booster doses of $BNT162b2_{SA}$ as rerandomized, have at least 1 valid and determinate immunogenicity result after Dose 4 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Population	Description
Dose 3 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 at initial randomization, receive a third dose of BNT162b2 or BNT162b2$_{SA}$ at rerandomization, and have at least 1 valid and determinate immunogenicity result after Dose 3.
Dose 4 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 at initial randomization, receive 2 booster doses of BNT162b2$_{SA}$ at rerandomization, and have at least 1 valid and determinate immunogenicity result after Dose 4.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
Evaluable efficacy (seroconversion)	All eligible randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window, have at least 1 N-binding antibody test result available at a post-Dose 2 visit, and have no other important protocol deviations as determined by the clinician prior to Dose 2.
Evaluable efficacy (asymptomatic surveillance)	All eligible randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window, consent to participate in the asymptomatic surveillance, and have no other important protocol deviations as determined by the clinician on or before the start of the asymptomatic surveillance period.
All-available efficacy	Dose 1 all-available: All randomized participants who receive at least 1 vaccination. Dose 2 all-available: All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention. Analyses of reactogenicity endpoints will be based on a subset of the safety population that includes participants with any e-diary data reported after vaccination.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Empirical RCDCs will be provided for all immunogenicity analyses.

Endpoint	Statistical Analysis Methods
Primary immunogenicity (Phase 3, boostability and protection against emerging VOCs)	In order to allow direct comparability with the reference strain, the anti-SA NTs may be adjusted to account for intrinsic variant or assay characteristics. The small group of existing Phase 3 participants who are to receive a third and fourth dose of BNT162b2$_{SA}$ will not be included in the primary and secondary analyses except for the last secondary descriptive objective. ***BNT162b2-Experienced Participants:*** **E1a: GMR of reference strain NT 1 month after the third dose of BNT162b2 at 30 µg to 1 month after the second dose of BNT162b2 in the same individuals** **E2a: GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** The comparisons of different NTs (anti-SA or anti–reference strain) or the same NTs at different time points within the same group will be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Endpoint	Statistical Analysis Methods
	limited to participants with nonmissing values at both time points or both NT measurements. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (eg, later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 97.5% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. Noninferiority of E1a and E2a will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.5. **E1b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 at 30 µg and 1 month after the second dose of BNT162b2 in the same individuals** **E2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** The percentages of participants with seroresponse at each time point and the difference in percentages will be provided. The 2-sided 97.5% CIs for the difference in percentages of participants with seroresponse will be calculated using the Miettinen and Nurminen method. Noninferiority of E1b and E2b will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%. ***BNT162b2-Naïve Participants:*** **N1a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2** For the between-group comparison, GMRs will be calculated as the mean of the difference of logarithmically transformed assay results between 2 groups and exponentiating the mean. The associated 2-sided 97.5% CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed titers and exponentiating the confidence limits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Endpoint	Statistical Analysis Methods
	Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.5. **N1b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2** The difference in percentages of participants with seroresponse and associated 2-sided 97.5% CIs will be calculated in the same way as for primary endpoints E1b and E2b. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%.
Secondary immunogenicity (Phase 3, boostability and protection against emerging VOCs)	***BNT162b2-Experienced Participants:*** **E3a: GMR of SA NT 1 month after the third dose of BNT162b2 at 30 µg to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** **E4a: GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 in the same individuals** **E3b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 at 30 µg and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** **E4b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2 in the same individuals** GMRs and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1a and E2a. If noninferiority of E1a and E2a are both established, E3a and E4a will be assessed sequentially using the same criterion (lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.5).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Endpoint	Statistical Analysis Methods
	The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. Similarly, if noninferiority of E1b and E2b are both established, E3b and E4b will be assessed sequentially using the same criterion (lower bound of the 2-sided 97.5% CI for the difference in percentages is greater than -10%). **GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 at 30 µg** **The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2 at 30 µg** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. **GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** **The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint E1a and E2a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. ***BNT162b2-Naïve Participants:*** **N2a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2**

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	N2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2 GMR and the associated 2-sided 97.5% CI will be calculated in the same way as for the primary endpoint N1a. Statistical superiority of N2a will be assessed if noninferiority of N1a is established. Superiority of N2a will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 1. The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. Statistical superiority of N2b will be assessed if noninferiority of N1b is established. Superiority of N2b will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than 0%. **GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2** **The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints E1b and E2b
Secondary immunogenicity (Phase 1)	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Endpoint	Statistical Analysis Methods
	• Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Endpoint	Statistical Analysis Methods
	GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the 16- to 25-year age group)	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and 2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment. The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years

This document can only be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Endpoint	Statistical Analysis Methods
	minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2: **GMTs/GMCs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level** GMTs/GMCs and 2-sided 95% CIs will be provided by initial vaccine and age group for the following time points: • At Dose 3 and 7 days and 1 month after Dose 3 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level** GMFRs from before Dose 3 to 7 days and 1 month after Dose 3 and 2-sided 95% CIs will be provided by initial vaccine and age group. GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Endpoint	Statistical Analysis Methods
	GMRs of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2 GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed reference-strain titers for each participant (1 month after Dose 3 – 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. **GMRs of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2** GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (SA-variant titer at 1 month after Dose 3 – reference-strain titer at 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.
Exploratory immunogenicity (Phase 2/3)	**GMTs/GMCs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers,

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Endpoint	Statistical Analysis Methods
	calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels after Dose 1 and after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Endpoint	Statistical Analysis Methods
Exploratory immunogenicity (Phase 3, boostability and protection against emerging VOCs)	**GMTs of SARS CoV-2 reference strain neutralizing titers in participants receiving a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$** GMTs and associated 2-sided 95% CIs at Dose 3 and each subsequent time point will be provided for each vaccine group and age group. **GMFRs of SARS CoV-2 reference strain neutralizing titers in participants receiving a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of BNT162b2$_{SA}$** GMFRs from Dose 3 to each subsequent time point and associated 2-sided 95% CIs will be provided for each vaccine group and age group. **Geometric mean NT for any VOC not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2** Geometric means and associated 2-sided 95% CIs of any anti-VOC neutralizing titers will be provided at each time point for each group.

9.4.2. Efficacy Analyses

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Endpoint	Statistical Analysis Methods
	Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.
Secondary	**First: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Second: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Third and fourth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Endpoint	Statistical Analysis Methods
	Fifth and sixth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints for COVID-19 illness according to CDC-defined symptoms will be evaluated descriptively with 95% CIs. **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days or from 14 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[10] Missing efficacy data will not be imputed. The following secondary efficacy endpoints regarding asymptomatic SARS-CoV-2 infection will be evaluated based on a success criterion of the lower bound of the 2-sided 95% CI for VE being >20%. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past**

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
the European Union
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Endpoint	Statistical Analysis Methods
	SARS-CoV-2 infection or confirmed COVID-19 for the active vaccine group to the placebo group VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate per 1000 person-years of follow-up in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The hypothesis will be tested if at least 206 cases are accrued. In addition, a descriptive summary of VE against asymptomatic infection over different time intervals (ie, prior to 1 month after Dose 2, from 1 month after Dose 2 onwards), along with the associated 2-sided 95% CI, will be calculated using the same method. The analysis of the primary definition of asymptomatic cases will be based on the evaluable efficacy (seroconversion) population and the Dose 2 all-available efficacy population. The analysis of the secondary definition of asymptomatic cases will be based on the Dose 1 all-available efficacy population. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants without evidence of infection (up to the start of asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The hypothesis will be tested if at least 53 cases are accrued. The analysis will be based on the evaluable efficacy (asymptomatic surveillance) population and the all-available efficacy population and will include only participants who are consented to participate in the asymptomatic surveillance and who do not have serological or virological evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
Exploratory	**Ratios of confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants without, and with and without, evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** After the primary objectives are met at the final analysis of at least 164 first primary cases, the study will continue with blinded follow-up until the participant is unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. A descriptive update of VE will be provided with additional follow-up data. VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[10] Supportive analysis of time to confirmed COVID-19 illness will be performed using Kaplan-Meier cumulative incidence curves. Participants who were randomized to placebo will be censored at the time of receipt of BNT162b2. **Incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness from 7 days after the second dose will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted. **Incidence of asymptomatic SARS-CoV-2 infection through the entire study follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants who received BNT162b2 and who have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for asymptomatic infection will be provided for participants who received BNT162b2 at initial randomization and have no serological or

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	virological evidence of past SARS-CoV-2 infection or confirmed COVID-19. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with evidence of infection (up to the start of the asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. Participants who are consented to participate in the asymptomatic surveillance and who have serological or virologic evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period will be included in the analysis.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[11] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group. AEs and SAEs reported during the open-label follow-up period will be summarized separately for participants who were unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. For Phase 3 participants enrolled for assessment of boostability and protection against emerging VOCs, descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for local reactions and systemic events from Day 1 through Day 7 after each dose, AEs from Dose 1 to 1 month after the last dose, and SAEs from Dose 1 to 5 or 6 months after the last dose. Local reactions and systemic events from Day 1 through Day 7 after each dose will be presented by severity and cumulatively across severity levels. The safety analyses are based on the safety population. Analyses of reactogenicity endpoints are based on a subset of the safety population that includes participants with any e-diary data reported after vaccination. Participants will be summarized by vaccine group

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Endpoint	Statistical Analysis Methods
	according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2: Descriptive statistics will be provided by initial vaccine and age group for local reactions and systemic events from Day 1 through Day 7 after Dose 3, and AEs/SAEs from Dose 3 to 1 month after Dose 3. Local reactions and systemic events from Day 1 through Day 7 after Dose 3 will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs.

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing “Process 1” and each lot of “Process 2” will be summarized descriptively. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing “Process 1” will be selected randomly for the analysis.

Exploratory analyses to investigate possible immunological correlates with efficacy, and characterization of infecting SARS-CoV-2 variants, may be conducted.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The cell-mediated immune response and additional humoral immune response parameters to the reference strain and SA will be summarized for the subset of participants with PBMC samples collected.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 6 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

This document cannot be used to support and marketing authorisation application and any extensions or variations thereof
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8, for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

Only the first primary endpoint will be analyzed at IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints (confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and in all participants, confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection and in all participants) will be evaluated sequentially in the stated order, by the same method used for the evaluation of primary VE endpoints. Success thresholds for secondary VE endpoints will be appropriately chosen to control overall type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Complete safety and immunogenicity analysis approximately 1 month after Dose 3 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

(with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.

- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.

- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.

- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2.

- Complete safety and immunogenicity analysis approximately 1 month after Dose 3 for Phase 3 participants included in the booster evaluation and approximately 1 month after Dose 2 for newly enrolled Phase 3 participants included in the BNT162b2$_{SA}$ evaluation.

- Analysis of efficacy against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) when a sufficient number of cases have accrued to evaluate the objective(s).

- Complete safety and efficacy analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.

- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort

- Review of safety data in the case of a stopping rule being met

- Review of safety and/or immunogenicity data to:

  - Allow groups of participants of 65 to 85 years of age to proceed

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review

- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Up until the final efficacy analysis, 3 blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial. When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. • Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCR	B-cell receptor
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
E1, E2, etc	vaccine-experienced (statistical tests)
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LL	lower limit

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Abbreviation	Term
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N1, N2, etc	vaccine-naïve (statistical tests)
N/A	not applicable
NAAT	nucleic acid amplification test
NI	noninferiority
non-S	nonspike protein
NT	neutralizing titer
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SA	South Africa
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Abbreviation	Term
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
TCR	T-cell receptor
UK	United Kingdom
ULN	upper limit of normal
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
VOC	variant of concern
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs after accrual of at least 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

10.9. Appendix 9: Genetics

Use/Analysis of DNA and/or RNA

- Genetic variation may impact a participant's response to study intervention, as well as susceptibility to and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA and/or RNA analysis.
- The results of genetic analyses may be reported in a CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA and/or RNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
  - Samples for specified genetic analysis (see Section 8.7) will be stored for up to 15 years or other period as per local requirements.
- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.

4 Centers for Disease Control and Prevention. Emerging SARS-CoV-2 variants. Available from: https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html. Updated: 28 Jan 2021. Accessed: 10 Feb 2021.

5 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

6 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

7 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

8 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

9 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

10 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

11 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 15 Clean Copy, 25Mar2021
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	25-Mar-2021 13:24:46	Final Approval
PPD	25-Mar-2021 13:38:04	Business Line Approver

090177e1969cd8c3\Approved\Approved On: 25-Mar-2021 13:38 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**

Protocol amendment 14	02 March 2021	• In order to further describe duration of protection, and heterologous/homologous protection against the emerging VOCs, an additional dose of BNT162b2 or BNT162b2$_{SA}$ will be given to approximately 600 Phase 3 participants approximately 5 to 7 months after their second dose of BNT162b2; a further dose of BNT162b2$_{SA}$ will be given to approximately 30 of those participants who receive BNT162b2$_{SA}$:
		  ◦ Added corresponding objectives, estimands, and endpoints
		  ◦ Added corresponding SoA and procedures
		  ◦ Added details in the statistical methods sections.
		• Approximately 300 BNT162b2-naïve participants will be enrolled and receive 2 doses of BNT162b2$_{SA}$ to describe heterologous/homologous protection against the emerging VOCs and reference strains:
		  ◦ Added corresponding objectives, estimands, and endpoints
		  ◦ Added corresponding SoA and procedures
		  ◦ Added details in the statistical methods sections.
		• Cell-mediated immune responses will also be described following isolations of PBMCs in a subset of both the Phase 3 participants who receive a single booster vaccination and the BNT162b2-naïve group who receive BNT162b2$_{SA}$.
		• Added the asymptomatic case definitions in Section 8.1 and further clarified the secondary definition for asymptomatic case based on seroconversion of N-binding antibody.
		• Defined the analysis populations used for evaluation of asymptomatic infection based on seroconversion of N-binding antibody and based on NAAT from participants who consent to active surveillance.
		• Clarified that unblinding for a nonemergency reason should be conducted outside of the IRT system.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified that if multiple visits occur on the same day, all procedures for all visits must be conducted (including collection of all blood samples). • Clarified the plan for stepwise unblinding of the sponsor in the study.

Protocol amendment 13	12 February 2021	• In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2:
		  • Added corresponding objectives, estimands, and endpoints
		  • Added corresponding SoA and procedures
		  • Added details in the statistical methods sections.
		• Clarified the population used for analysis of reactogenicity endpoints.
		• To align with current recommendations, investigators may exercise judgment on review of inclusion and exclusion criteria ahead of vaccination with BNT162b2 for participants who originally received placebo.
		• Clarified that if a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent.
		• Participants who provide biweekly swabs for surveillance of asymptomatic infection should now continue to swab even after unblinding if they originally received BNT162b2, to maximize the numbers of swabs to be collected.
		• Clarified the procedures for unscheduled visits to administer a second dose in the event a participant received only 1 dose of BNT162b2.

Protocol amendment 12	14 January 2021	• Because of a formatting error in protocol amendment 11, exclusion criterion 4 was inadvertently added to exclusion criterion 3 and the subsequent criteria renumbered. This amendment corrects that error. • Because of a change in the pace with which participants ≥16 years of age who originally received placebo will become eligible for receipt of BNT162b2, text was updated throughout the protocol to reflect that this will happen in a phased manner, with recommendations detailed

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		separately and available in the electronic study reference portal. • Clarified that participants who are unblinded because they become potentially eligible for receipt of BNT162b2 will not participate in surveillance for asymptomatic SARS CoV-2 infection. • Corrected the exploratory objective to describe non-S seroconversion to SARS-CoV-2 to clarify that this will only include participants who received BNT162b2 at initial randomization (since those who received it subsequently do not have blood drawn). • In line with current recommendations, removed the requirement to discontinue study intervention because of a diagnosis of COVID-19 during the study.

Protocol amendment 11	04 January 2021	• Added approaches to evaluate efficacy against asymptomatic SARS-CoV-2 infection:
		  • Added objectives, estimands, and endpoints, and statistical methods, for assessment via N-binding antibody seroconversion;
		  • Added a potential intensive surveillance period for nasal swabbing, for assessment via NAAT:
		  • Corresponding objectives, estimands, and endpoints added
		  • Corresponding SoA and procedures added
		  • Details added in the statistical methods sections.
		• Added the possibility of assessing full-length S-binding, instead of S1-binding, IgG levels in Phase 2/3.
		• Clarified in Section 4.1.1 that any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity at the approximate time participants in Phase 2/3 reach Visit 4, for consistency with other sections.
		• Added a sentence to reflect that assent is obtained from participants <18 years of age.

Protocol amendment 10	01 December 2020	• Added the possibility of administering BNT162b2 to participants who originally received placebo, following any local or national recommendations. • Added the possibility of administering BNT162b2 to participants who originally

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		received placebo, following completion of the active safety surveillance period. • Added corresponding exploratory objectives and statistical analysis details. • Removed immunogenicity analyses of titers greater than defined threshold(s). • Removed the need for blinded COVID-19 case review after the final efficacy analysis. • Included the possibility, due to local circumstances related to the COVID-19 pandemic, that study procedures that do not require in-person participant contact may be performed by telehealth. • In light of additional information to better estimate the standard deviation of SARS-CoV-2 neutralizing titers, increased the sample size for the noninferiority immunogenicity analysis in adolescents 12 to 15 years of age.
Protocol amendment 9	29 October 2020	• To better align with the natural history of SARS-CoV-2 infection, added Phase 2/3 secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days after the second dose; also modified the existing secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days, as well as 7 days, after the second dose; • Made corresponding changes to the study design, study assessments and procedures, and statistical analysis sections. • For operational reasons, removed the interim analysis planned after accrual of 32 cases. • Clarified that interim analyses will be conducted after accrual of *at least* 62, 92, and 120 cases. • Included any participants 16 through 17 years of age enrolled under this amendment in the reactogenicity subset. • Added an unblinded clinical scientist to support DMC activities. • Clarified that serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.
Protocol amendment 8	15 October 2020	• Removed “N-binding antibody” and “SARS-CoV-2 detection by NAAT” as endpoints from the third exploratory objective, as these results are used for the determination of the population, and are not endpoints.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified that the "Process 1" participants included in the descriptive analysis of "Process 1"- and "Process 2"-manufactured study interventions will be selected randomly. • Clarified that surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study. • Further modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Clarified that for participants who are not in the reactogenicity subset, local reactions and systemic events following vaccination should be detected and reported as AEs. • Clarified that premenarchal females are not WOCBP. • Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2. • Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2." • Clarified the degree of unblinding on the unblinded submissions team in Section 6.3.3. • Made provision for a second dose of BNT162b2 in participants who were affected by a medication error at Visit 2 in Section 6.6. • Provided further clarification regarding discontinuation of study intervention in Section 7.1. • Modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Added that 2 periods of potential COVID-19 symptoms within 4 days will be considered as a single illness. • Provided guidance in Section 8.13 regarding circumstances in which a SARS-CoV-2 test

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		might be required even if symptoms within 7 days following each vaccination are considered more likely due to vaccine reactogenicity. • Made allowance in Section 8.13 for a second SARS-CoV-2 test to be performed within the same potential COVID-19 illness if it is in accordance with routine practice. • Added Section 8.15 to describe the reporting of SARS-CoV-2 test results and their implications for participants receiving a second vaccine dose. • Added statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age. • Amended scope of analyses of safety data in Section 9.5.1. • Made various editorial changes.
Protocol amendment 6 (Germany-specific)	23 September 2020	• According to regulatory request, inclusion criterion 1 now specifies that participants less than 18 years of age will not be enrolled in the EU.
Protocol amendment 6	08 September 2020	• Reordered some procedures in the Phase 2/3 schedule of activities for consistency with the main body of the protocol. • Corrected the window for the 6-month follow-up visit to be approximately 6 months after Vaccination 2. • Reduced the volume of blood draws to ~20 mL. • Removed the need to have safety data reported for participants to be included in the safety objective assessment. • Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease. • Increased the sample size for Phase 2/3 to ~43,998. • Clarified that inclusion criterion 4 (ie, participants at higher risk for acquiring COVID-19) is applicable for Phase 2/3 only, and provided some examples. • Removed exclusion criterion 2 (ie, known infection with HIV, HCV, or HBV) for Phase 3 and added criteria for HIV-positive participants. • Decreased the lower age limit and removed the upper age limit for inclusion in Phase 2/3 in order to evaluate BNT162b2 30 µg in older adolescents and those over 85 years of age;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		updated the title and other references to adults to align with this change. • Renamed the immunological assays to align with other program-level documents. • Removed reference to the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) being "heads up." • Clarified that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention. • Added clarification that potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. • Updated the analysis population descriptions to align with the study SAP.
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory. • Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7. • Updated the stopping and alert rule parameters for enhanced COVID-19.
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation, and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol. • To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial • Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 20
LIST OF FIGURES 21
1. PROTOCOL SUMMARY 22
1.1. Synopsis 22
1.2. Schema 36
1.3. Schedule of Activities 37
1.3.1. Phase 1 37
1.3.2. Phase 2/3 44
1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo 48
1.3.4. Administration of an Additional Dose of BNT162b2 or BNT162b2$_{SA}$ 50
1.3.5. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants 53
1.3.6. Surveillance for Asymptomatic SARS-CoV-2 Infection 56
2. INTRODUCTION 57
2.1. Study Rationale 57
2.2. Background 57
2.2.1. Clinical Overview 59
2.3. Benefit/Risk Assessment 59
2.3.1. Risk Assessment 61
2.3.2. Benefit Assessment 63
2.3.3. Overall Benefit/Risk Conclusion 63
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 63
3.1. For Phase 1 63
3.2. For Phase 2/3 65
4. STUDY DESIGN 72
4.1. Overall Design 72
4.1.1. Phase 1 73
4.1.2. Phase 2/3 74
4.2. Scientific Rationale for Study Design 77
4.3. Justification for Dose 77
4.4. End of Study Definition 78

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

5. STUDY POPULATION 79
5.1. Inclusion Criteria 79
5.2. Exclusion Criteria 80
5.3. Lifestyle Considerations 82
5.3.1. Contraception 82
5.4. Screen Failures 83
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 83
6. STUDY INTERVENTION 84
6.1. Study Intervention(s) Administered 84
6.1.1. Manufacturing Process 85
6.1.2. Administration 85
6.2. Preparation/Handling/Storage/Accountability 86
6.2.1. Preparation and Dispensing 87
6.3. Measures to Minimize Bias: Randomization and Blinding 88
6.3.1. Allocation to Study Intervention 88
6.3.2. Blinding of Site Personnel 88
6.3.3. Blinding of the Sponsor 88
6.3.4. Breaking the Blind 90
6.4. Study Intervention Compliance 90
6.5. Concomitant Therapy 91
6.5.1. Prohibited During the Study 91
6.5.2. Permitted During the Study 92
6.6. Dose Modification 92
6.7. Intervention After the End of the Study 93
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 93
7.1. Discontinuation of Study Intervention 93
7.2. Participant Discontinuation/Withdrawal From the Study 94
7.2.1. Withdrawal of Consent 94
7.3. Lost to Follow-up 95
8. STUDY ASSESSMENTS AND PROCEDURES 95

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorization application and any extensions or variations thereof
ema.europa.eu

8.1. Efficacy and/or Immunogenicity Assessments 97
8.1.1. Efficacy Against COVID-19 97
8.1.2. Efficacy Against Asymptomatic SARS-CoV-2 Infection 99
8.1.2.1. Seroconversion of N-Binding Antibody 99
8.1.2.2. NAAT-Confirmed SARS-CoV-2 Infection 99
8.1.3. Vaccine-Induced Immunogenicity....100
8.1.4. Biological Samples 100
8.1.5. Surveillance for Asymptomatic SARS-CoV-2 Infection 100
8.2. Safety Assessments 101
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 101
8.2.2. Electronic Diary....102
8.2.2.1. Grading Scales....103
8.2.2.2. Local Reactions 103
8.2.2.3. Systemic Events....104
8.2.2.4. Fever....105
8.2.2.5. Antipyretic Medication 105
8.2.3. Phase 1 Stopping Rules 105
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 107
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 107
8.2.6. Pregnancy Testing 108
8.3. Adverse Events and Serious Adverse Events....108
8.3.1. Time Period and Frequency for Collecting AE and SAE Information....108
8.3.1.1. Reporting SAEs to Pfizer Safety....109
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF....110
8.3.2. Method of Detecting AEs and SAEs 110
8.3.3. Follow-up of AEs and SAEs....110
8.3.4. Regulatory Reporting Requirements for SAEs....110
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 111
8.3.5.1. Exposure During Pregnancy....111
8.3.6. Exposure During Breastfeeding....112

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

8.3.6.1. Occupational Exposure 113
8.3.7. Cardiovascular and Death Events 113
8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 113
8.3.9. Adverse Events of Special Interest 114
8.3.9.1. Lack of Efficacy 114
8.3.10. Medical Device Deficiencies 114
8.3.11. Medication Errors 114
8.4. Treatment of Overdose 115
8.5. Pharmacokinetics 116
8.6. Pharmacodynamics 116
8.7. Genetics 116
8.8. Biomarkers 116
8.9. Immunogenicity Assessments 116
8.10. Health Economics 116
8.11. Study Procedures 116
8.11.1. Phase 1 116
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 116
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 118
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 120
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 121
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 122
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 124
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 126
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 127
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4) 127
8.11.1.10. Between Visits 8 and 9 128

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2) 128
8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a)....130
8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a)....130
8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2....131
8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2....132
8.11.2. Phase 2/3....132
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 132
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 135
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)....137
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)....138
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 138
8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 139
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 140
8.13. COVID-19 Surveillance (All Participants) 141
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 142
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)....143
8.14. Communication and Use of Technology....144
8.15. SARS-CoV-2 NAAT Results....144

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo 145
8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2) 145
8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101) 147
8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102) 148
8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102) 148
8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102) 149
8.17. Administration of an Additional Dose of BNT162b2 or BNT162b2$_{SA}$ 149
8.17.1. Visit 301 – Vaccination 3: (150 to 210 Days After Visit 2) 149
8.17.2. Visit 302 – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 301) 152
8.17.3. Visit 303 – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 301) 152
8.17.4. Visit 304 – 1-Week Follow-up Visit (Vaccination 4): (6 to 8 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$ 154
8.17.5. Visit 305 – 1-Month Follow-up Visit (Vaccination 4): (28 to 35 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$ 155
8.17.6. Visit 306 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 301): 155
8.17.7. Visit 307 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 301): 156
8.18. Administration of BNT162b2$_{SA}$ to BNT162b2-naïve Participants 156
8.18.1. Visit 401 – Vaccination 1: (Day 1) 156
8.18.2. Visit 402 – Vaccination 2: (19 to 23 Days After Visit 401) 159
8.18.3. Visit 403 – 1-Week Follow-up Visit (After Vaccination 2): (6 to 8 Days After Visit 402) 161
8.18.4. Visit 404 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 402) 161
8.18.5. Visit 405 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 402) 162

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

8.18.6. Visit 406 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 402) 163
8.19. Surveillance for Asymptomatic SARS-CoV-2 Infection 163
8.19.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11 163
8.19.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection 164
9. STATISTICAL CONSIDERATIONS 165
9.1. Estimands and Statistical Hypotheses 165
9.1.1. Estimands 165
9.1.2. Statistical Hypotheses 166
9.1.2.1. Statistical Hypothesis Evaluation for Efficacy 166
9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity 166
9.2. Sample Size Determination 168
9.2.1. Phase 1 168
9.2.2. Efficacy Against COVID-19 168
9.2.3. Efficacy Against Asymptomatic Infection 169
9.2.4. Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years 169
9.2.5. Boostability and Protection Against Emerging SARS-CoV-2 VOCs 169
9.2.6. Safety 170
9.3. Analysis Sets 172
9.4. Statistical Analyses 174
9.4.1. Immunogenicity Analyses 174
9.4.2. Efficacy Analyses 184
9.4.3. Safety Analyses 189
9.4.4. Other Analyses 191
9.5. Interim Analyses 191
9.5.1. Analysis Timing 194
9.6. Data Monitoring Committee or Other Independent Oversight Committee 195
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 197
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 197

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

10.1.1. Regulatory and Ethical Considerations 197
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 197
10.1.2. Informed Consent Process 198
10.1.3. Data Protection 199
10.1.4. Dissemination of Clinical Study Data 199
10.1.5. Data Quality Assurance 200
10.1.6. Source Documents 202
10.1.7. Study and Site Start and Closure 202
10.1.8. Sponsor's Qualified Medical Personnel 203
10.2. Appendix 2: Clinical Laboratory Tests 204
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 206
10.3.1. Definition of AE 206
10.3.2. Definition of SAE 207
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 209
10.3.4. Reporting of SAEs 212
10.4. Appendix 4: Contraceptive Guidance 213
10.4.1. Male Participant Reproductive Inclusion Criteria 213
10.4.2. Female Participant Reproductive Inclusion Criteria 213
10.4.3. Woman of Childbearing Potential 214
10.4.4. Contraception Methods 215
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 217
10.6. Appendix 6: Abbreviations 219
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 223
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection 226
11. REFERENCES 227

LIST OF TABLES

Table 1. Local Reaction Grading Scale 103
Table 2. Systemic Event Grading Scale 104

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Table 3. Scale for Fever 105
Table 4. Power Analysis for Noninferiority Assessment 169
Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 171
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility 192
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses 193
Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall 193
Table 9. Laboratory Abnormality Grading Scale 204
Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 224
Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 225

LIST OF FIGURES

Figure 1. Multiplicity Scheme 168

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 3 antigens:

BNT162b1 (variant RBP020.3): a modRNA encoding the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5);

BNT162b2 (variant RBP020.2): a modRNA encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9);

BNT162b2s01 (variant RBP020.11): a modRNA encoding the P2 S containing South Africa B.1.351 variant-specific mutations, hereafter referred to as BNT162b2$_{SA}$, as a representative variant of concern (VOC).

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and/or efficacy of these prophylactic BNT162 vaccines against COVID-19.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	• GMC/GMT and GMFR at the time of Dose 3 and 7 days and 1 month after Dose 3. • GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2 • GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2.	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof are expressly excluded

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the safety and tolerability profile of BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants, or as 2 doses to BNT162b2-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2-experienced participants	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 5 or 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary Immunogenicity ***BNT162b2-experienced participants***		
To demonstrate the noninferiority of the anti–reference strain immune response after a third dose of BNT162b2 compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after the third dose of BNT162b2 to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate the noninferiority of the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
BNT162b2-experienced participants		
To demonstrate the noninferiority of the anti-SA immune response after a third dose of BNT162b2 compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the third dose of BNT162b2 to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti–reference strain immune response after 1 dose of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ and a third dose of BNT162b2	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2	SARS-CoV-2 SA NT in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$ or the third dose of BNT162b2) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Objectives[a]	Estimands	Endpoints
To descriptively compare the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ and the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate a statistically greater anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 SA NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
To descriptively compare the anti–reference strain immune response after 2 doses of BNT162b2$_{SA}$ and after 2 doses of BNT162b2	GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization	In participants who received BNT162b2 at initial randomization: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate and characterize the SARS-CoV-2 isolate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers • Identification of SARS-CoV-2 variant(s)
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers
To describe the immune response to any VOCs not already specified	Geometric mean NT for any VOCs not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2	• SARS-CoV-2 NTs for any VOCs not already specified

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and SA in a subset of participants: • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 2 doses to BNT162b2-naïve participants • 7 Days and 1 and 6 months after BNT162b2 given as a third dose to BNT162b2-experienced participants		

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for a description of the manufacturing process.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants ≥16 years of age who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants who will receive a third dose of BNT162b2 or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ (based upon the South African variant and hereafter referred to as BNT162b2$_{SA}$).

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof are europages.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

For evaluation of boostability and protection against emerging VOCs, 600 existing Phase 3 participants 18 to 55 years of age will be rerandomized in a 1:1 ratio to receive either a third dose of BNT162b2 or a third dose of BNT162b2$_{SA}$.

An additional group of 30 existing Phase 3 participants 18 to 55 years of age will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$. For these 30 participants, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the investigator and sponsor will not be. Serum samples from these participants may be used for assay development purposes and, except for objectives relating to response to a fourth dose, their results will be analyzed separately from the main immunogenicity analyses.

Three hundred participants 18 to 55 years of age who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19 will be enrolled as a new cohort of participants to receive BNT162b2$_{SA}$ given as a 2-dose series.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg
- BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S containing South Africa B.1.351 variant–specific mutations): 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated. VE will be demonstrated if the lower bound of the 95% CI for VE is >20%.

In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

The boostability and protection against emerging VOCs for BNT162b2-experienced participants and BNT162b2-naïve participants will be assessed based on GMRs of SARS-CoV-2 SA-neutralizing and/or reference strain–neutralizing titers using a 2-fold noninferiority margin and the difference in percentages of participants with seroresponse using a 10% noninferiority margin.

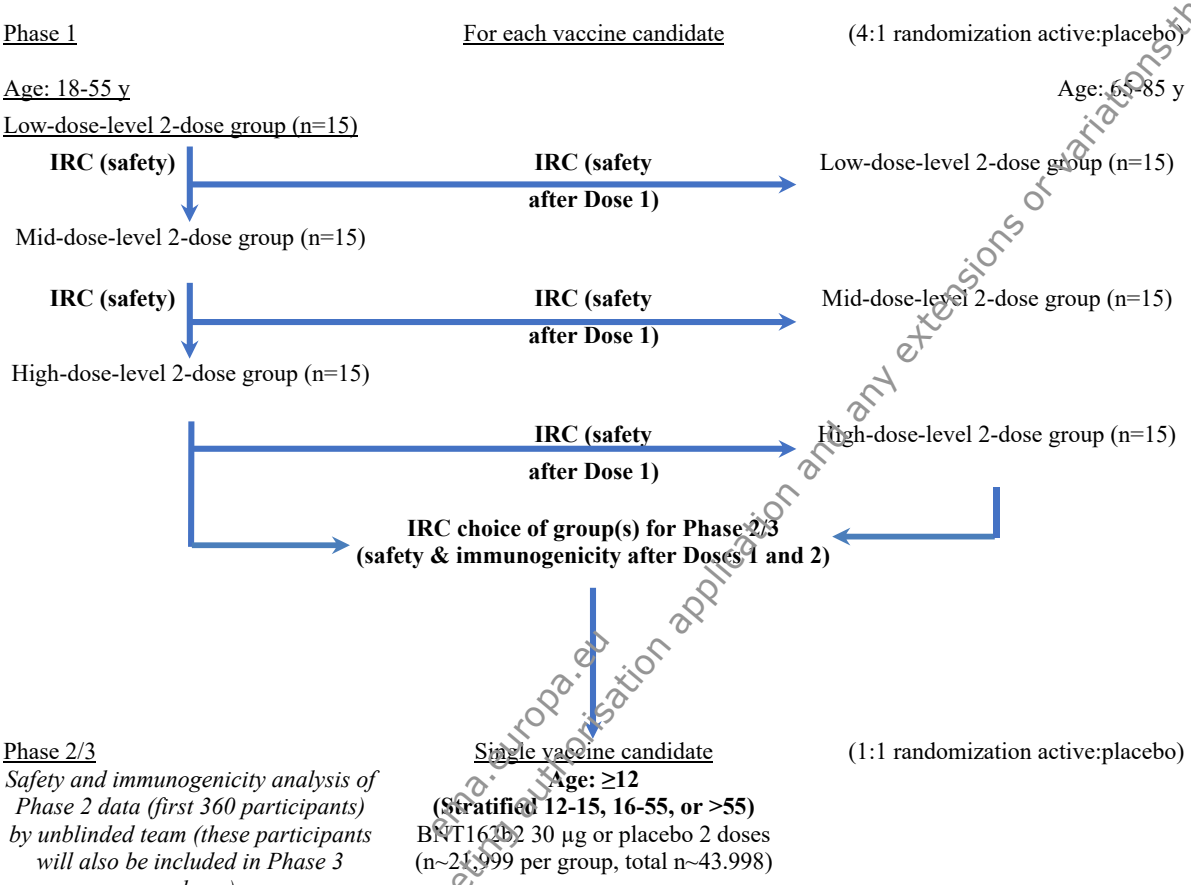
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

Except for the objectives to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age and evaluation of boostability and protection against emerging VOCs by BNT162b2 and BNT162b2$_{SA}$ in Phase 3, the other immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMR, and the associated 95% CIs, for SARS-CoV-2 neutralizing titers, full-length S-binding or S1-binding IgG levels, and/or RBD-binding IgG levels (Phase 1 only) at the various time points.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

1.2. Schema



Abbreviation: IRC = internal review committee.

Note: Participants ≥16 years of age who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

1.3. Schedule of Activities

The SoA tables provide an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b1 or BNT162b2 (at any dose level) will continue in the study as originally planned.

All other participants will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study no later than at the approximate time participants in Phase 2/3 reach Visit 4. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X								*Continued on table below*		
Assign participant number	X										
Obtain demography and medical history data	X										
Obtain details of medications currently taken	X										
Perform physical examination	X	X	X	X	X	X	X				
Measure vital signs (including body temperature)	X	X	X	X	X	X	X				
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL					
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL										
Serological test for prior COVID-19 infection	~20 mL										
Perform urine pregnancy test (if appropriate)	X	X			X						
Obtain nasal (midturbinate) swab(s)[c]		X			X					X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X			
Confirm eligibility	X	X			X						
Collect prohibited medication use			X	X	X	X	X	X		X	X

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Review hematology and chemistry results		X		X	X	X	X		*Continued on table below*		
Review temporary delay criteria		X			X						
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X			
Obtain randomization number and study intervention allocation		X									
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL			~20 mL
Administer study intervention		X			X						
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X									
Provide thermometer and measuring device		X			X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►		◄	———	►			

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X		*Continued on table below*		
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X		X	X
Collect e-diary or assist the participant to delete application											
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)										X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg **Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9**			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**			
Obtain informed consent		X						
Confirm participant originally received 10 to 30 µg of BNT162b1 or BNT162b2		X						
Perform urine pregnancy test (if appropriate)		X						
Confirm use of contraceptives (if appropriate)		X	X	X				
Collect prohibited medication use	X	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X				
Measure body temperature		X						
Confirm eligibility		X						
Review temporary delay criteria		X						
Collect blood sample for immunogenicity assessment	~20 mL	~20 mL	~20 mL	~20 mL	~20 mL	~20 mL		~20 mL

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg **Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9**			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**			
Obtain nasal (midturbinate) swab(s)		X					X	
Obtain the participant's vaccine vial allocation using the IRT system		X						
Administer 30-µg dose of BNT162b2		X						
Assess acute reactions for at least 30 minutes after study intervention administration		X						
Provide thermometer and measuring device		X						
Remind participant of e-diary technologies		X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		←	→					

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg **Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9**			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**			
Review ongoing reactogenicity e-diary symptoms and obtain stop dates				X				
Collect AEs and SAEs as appropriate	X	X	X	X	X[b]	X[b]	X	X
Collect e-diary or assist the participant to delete application						X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: IRT = interactive response technology; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation applications and any extensions or variations thereof
ema.europa.eu

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant ≥16 years of age becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b2 or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b2 will continue in the study as originally planned.

All other participants ≥16 years of age who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4). If they want to receive BNT162b2, they will be unblinded and those who did originally receive placebo will move to the SoA in Section 1.3.3 for their remaining visits.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X		
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL		~20 mL/ ~10 mL
Obtain nasal (midturbinate) swab	X	X					X	
Obtain randomization number and study intervention allocation	X							
Administer study intervention	X	X						

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	◄►	◄►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X	X[f]
According to eligibility, ascertain willingness to receive BNT162b2 if originally received placebo; if willing, unblind the participant's study intervention assignment (if not already done), and move placebo recipients to the SoA in Section 1.3.3			X ◄►	X				
Collect e-diary or assist the participant to delete application						X		

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants ≥16 years of age who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. Any placebo recipient ≥16 years of age who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2.

Visit Number	101	102	103	104	105	Unplanned	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm participant meets local/national recommending criteria or is at least 175 days after Vaccination 2 (Visit 4/Visit 2)	X						
Obtain informed consent	X						
Confirm participant originally received placebo	X						
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X					
Collect prohibited medication use	X	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X		
Review and consider eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment	~20 mL						~20 mL
Obtain nasal (midturbinate) swab	X	X				X	
Obtain vaccine vial allocation via IRT	X	X					
Administer BNT162b2	X	X					

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	101	102	103	104	105	Unplanned	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Collect AEs and SAEs as appropriate	X	X	X	X		X[d]	X[d]
Contact the participant by telephone			X	X	X		
Request the participant return the e-diary or assist the participant to delete the application					X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)						X	X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

a. For participants who become eligible according to recommendations detailed separately and available in the electronic study reference portal.
b. For any remaining Phase 2/3 placebo recipients who wish to receive BNT162b2; may be combined with Visit 4 for Phase 2/3 participants.
c. Only if the participant has no blood sample collected in the previous 7 days.
d. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.4. Administration of an Additional Dose of BNT162b2 or BNT162b2$_{SA}$

Select participants in Phase 3 at select sites who originally received 2 doses of BNT162b2 will be offered the opportunity to receive a third (and potentially fourth) dose of BNT162b2 or BNT162b2$_{SA}$.

Visit Number	301	302	303	304	305	306	307	Unplanned	Unplanned
Visit Description	Vax 3[a]	1-Week Follow-up Visit (After Vax 3)	1-Month Follow-up Visit (After Vax 3)	1-Week Follow-up Visit (After Vax 4)[b]	1-Month Follow-up Visit (After Vax 4)[b]	6-Month Follow-up Visit	18-Month Follow-up Visit	Potential COVID-19 Illness Visit[c]	Potential COVID-19 Convalescent Visit
Visit Window (Days)	150 to 210 Days After Visit 2	6 to 8 Days After Visit 301	28 to 35 Days After Visit 301	6 to 8 Days After Visit 303	28 to 35 Days After Visit 303	175 to 189 Days After Visit 301	532 to 560 Days After Visit 301	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4					
Obtain informed consent	X								
Confirm participant originally received BNT162b2 at Dose 1 and Dose 2	X								
Perform urine pregnancy test (if appropriate)	X		X[b]						
Confirm use of contraceptives (if appropriate)	X	X	X	X	X				
Collect prohibited medication use	X	X	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X	X	X			
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X			X	X		
Measure body temperature	X		X[b]						
Confirm eligibility	X		X[b]						

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Visit Number	301	302	303	304	305	306	307	Unplanned	Unplanned
Visit Description	**Vax 3[a]**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**1-Week Follow-up Visit (After Vax 4)[b]**	**1-Month Follow-up Visit (After Vax 4)[b]**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[c]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**150 to 210 Days After Visit 2**	**6 to 8 Days After Visit 301**	**28 to 35 Days After Visit 301**	**6 to 8 Days After Visit 303**	**28 to 35 Days After Visit 303**	**175 to 189 Days After Visit 301**	**532 to 560 Days After Visit 301**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			**ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4**					
Review temporary delay criteria	X		X[b]						
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL		~20 mL
Collect blood sample for PBMC isolation[d]	~120 mL	~120 mL	~120 mL			~120 mL			
Collect blood sample for HLA typing[d]	~5 mL								
Obtain nasal (midturbinate) swab(s)	X		X[b]					X	
Obtain randomization number and study intervention allocation using the IRT system	X								
Administer study intervention	X		X[b]						
Assess acute reactions for at least 30 minutes after study intervention administration	X		X[b]						
Provide thermometer and measuring device	X								
Remind participant of e-diary technologies	X		X[b]						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	◄	———	►	◄	►				

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document can be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	301	302	303	304	305	306	307	Unplanned	Unplanned
Visit Description	**Vax 3[a]**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**1-Week Follow-up Visit (After Vax 4)[b]**	**1-Month Follow-up Visit (After Vax 4)[b]**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[c]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**150 to 210 Days After Visit 2**	**6 to 8 Days After Visit 301**	**28 to 35 Days After Visit 301**	**6 to 8 Days After Visit 303**	**28 to 35 Days After Visit 303**	**175 to 189 Days After Visit 301**	**532 to 560 Days After Visit 301**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
	ONLY FOR SELECT PARTICIPANTS AT SELECT SITES WHO ORIGINALLY RECEIVED BNT162b2 AT DOSE 1 AND DOSE 2			**ONLY FOR THE SUBSET OF PARTICIPANTS WHO RECEIVE DOSE 4**					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates			X		X				
Collect AEs and SAEs as appropriate	X	X	X	X	X	X[e]	X[e]	X	X[e]
Collect e-diary or assist the participant to delete application							X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)								X	X

Abbreviations: e-diary = electronic diary; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; vax = vaccination.

a. Visit 301 can occur on the same day as Visit 4, but all procedures for both visits must be conducted (including collection of all blood samples).
b. Only for those participants who will receive Dose 4.
c. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
d. Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants who will receive a third (but not fourth) dose of BNT162b2 or BNT162b2(S) at select sites only.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.5. Administration of BNT162b2$_{SA}$ to BNT162b2-Naïve Participants

As part of Amendment 14, an additional cohort of BNT162b2-naïve participants will be enrolled to receive BNT162b2$_{SA}$ per the following SoA.

Visit Number	401	402	403	404	405	406	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X	X				
Collect nonstudy vaccine information	X	X	X	X	X			
Collect prohibited medication use		X	X	X	X	X	X	X
For participants who are HIV+ positive, record latest CD4 count and HIV viral load	X			X	X	X		
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment	~50 mL		~50 mL	~50 mL	~50 mL	~50 mL		~20 mL
Collect blood sample for PBMC isolation[d]	~120 mL		~120 mL	~120 mL	~120 mL			
Collect blood sample for HLA typing[d]	~5 mL							

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Visit Number	401	402	403	404	405	406	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain nasal (midturbinate) swab	X	X					X	
Obtain the participant's vaccine vial allocation using the IRT system	X	X						
Administer BNT162b2$_{SA}$	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	◄►	◄►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X		X				
Collect AEs and SAEs as appropriate	X	X	X	X	X[e]	X[e]	X	X[e]
Collect e-diary or assist the participant to delete application						X		

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Visit Number	401	402	403	404	405	406	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[b]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[a]**	**19 to 23 Days After Visit 401**	**6 to 8 Days After Visit 402**	**28 to 35 Days After Visit 402**	**175 to 189 Days After Visit 402**	**532 to 560 Days After Visit 402**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: e-diary = electronic diary; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; vax = vaccination.

a. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
b. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
c. Including, if indicated, a physical examination.
d. Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants at select sites only.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.6. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4 or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

Visit Number	201	202 Onward
Visit Description	**Asymptomatic SARS-CoV-2 Infection Surveillance Consent**	**Asymptomatic SARS-CoV-2 Infection Surveillance Swab**
Visit Window (Days)	**From Approval of Protocol Amendment 11**	**Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection**
Obtain informed consent for asymptomatic SARS-CoV-2 infection surveillance	X	
Collect prohibited medication use	X	
Collect blood sample for immunogenicity assessment[a]	~20 mL/~10 mL	
Obtain nasal (midturbinate) swab (self-swab at home or by site staff at an in-person visit)	X	X
Collect AEs and SAEs as appropriate[b]	X	

a. Only if the participant has no blood sample collected in the previous 7 days. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
b. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no licensed vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

As more data about COVID-19 continue to accrue, the potential duration of protection afforded after a wild-type SARS-CoV-2 infection, and by vaccination, remains unknown. In addition, mutated SARS-CoV-2 VOCs have started to emerge, for example in the UK (known as 20I/501Y.V1, VOC 202012/01, or B.1.1.7), SA (known as 20H/501Y.V2 or B.1.351), and Brazil (known as P.1).[4]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[5,6]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Three SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 3 antigens:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5);

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9);

- **BNT162b2s01** (variant RBP020.11): nucleoside-modified messenger RNA (modRNA) as above, but encoding the P2 S containing South Africa B.1.351 variant–specific mutations, hereafter referred to as BNT162b2$_{SA}$, as a representative variant of concern (VOC).

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

In light of the unknowns regarding duration of protection, as well as the emerging VOCs, it is important to understand the boostability of BNT162, and potential heterologous protection against emerging VOC(s). A first step to address this will be to study an additional dose of BNT162b2 at 30 µg given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants who will receive a third dose of BNT162b2 or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ (based upon the South African variant and hereafter referred to as BNT162b2$_{SA}$).

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[7] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[8] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with the currently available therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.

- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.

- All participants 12 to 15 years of age will be included in the reactogenicity subset (see Section 8.2.2).

This document cannot be used to support a marketing authorisation application or any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[9]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of an efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	• GMC/GMT and GMFR at the time of Dose 3 and 7 days and 1 month after Dose 3.	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels
	• GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers
	• GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Objectives	Estimands	Endpoints
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Objectives[a]	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants, or as 2 doses to BNT162b2-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2-experienced participants	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 5 or 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary Immunogenicity ***BNT162b2-experienced participants***		
To demonstrate the noninferiority of the anti–reference strain immune response after a third dose of BNT162b2 compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after the third dose of BNT162b2 to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Objectives[a]	Estimands	Endpoints
BNT162b2-naïve participants		
To demonstrate the noninferiority of the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
BNT162b2-experienced participants		
To demonstrate the noninferiority of the anti-SA immune response after a third dose of BNT162b2 compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the third dose of BNT162b2 to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Objectives[a]	Estimands	Endpoints
To demonstrate the noninferiority of the anti–reference strain immune response after 1 dose of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ and a third dose of BNT162b2	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2	SARS-CoV-2 SA NT in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$ or the third dose of BNT162b2) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ and the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate a statistically greater anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 SA NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
To descriptively compare the anti–reference strain immune response after 2 doses of BNT162b2$_{SA}$ and after 2 doses of BNT162b2	GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Objectives[a]	Estimands	Endpoints
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization	In participants who received BNT162b2 at initial randomization: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate and characterize the SARS-CoV-2 isolate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers • Identification of SARS-CoV-2 variant(s)
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers
To describe the immune response to any VOCs not already specified	Geometric mean NT for any VOCs not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2	• SARS-CoV-2 NTs for any VOCs not already specified
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and SA in a subset of participants: • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 2 doses to BNT162b2-naïve participants • 7 Days and 1 and 6 months after BNT162b2 given as a third dose to BNT162b2-experienced participants		

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objectives.
b. See Section 6.1.1 for description of the manufacturing process.

Up until the final efficacy analysis, this protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants who will receive a third dose of BNT162b2 or a

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ (based upon the South African variant and hereafter referred to as BNT162b2$_{SA}$).

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than at the approximate time participants in Phase 2/3 reach Visit 4.

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162.

Participants are expected to participate for up to a maximum of approximately 26 months.

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 280 participants from each of the 2 age groups (12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

For evaluation of boostability and protection against emerging VOCs, 600 existing Phase 3 participants 18 to 55 years of age will be rerandomized in a 1:1 ratio to receive either a third dose of BNT162b2 or a third dose of BNT162b2$_{SA}$.

An additional group of 30 existing Phase 3 participants 18 to 55 years of age will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$. For these 30 participants, through 1 month

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

after their first dose of BNT162b2$_{SA}$ the participant will be blinded to their vaccine allocation but the investigator and Sponsor will not be. Serum samples from these participants may be used for assay development purposes and, except for objectives relating to response to a fourth dose, their results will be analyzed separately from the main immunogenicity analyses.

Three hundred participants 18 to 55 years of age who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19 will be enrolled as a new cohort of participants to receive BNT162b2$_{SA}$ given as a 2-dose series.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Participants ≥16 years of age who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 2/3 placebo recipient ≥16 years of age who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4).

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

The changes to the protocol as part of protocol amendment 14 to assess boostability and homologous/heterologous protection against emerging VOCs allow the evaluation of safety and immunogenicity of BNT162b2$_{SA}$:

- When given as a third dose to C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously (ie, BNT162b2-experienced) and have not experienced COVID-19.
- In a small separate group of individuals who previously received 2 doses of BNT162b2 followed by 1 dose of BNT162b2$_{SA}$, a second BNT162b2$_{SA}$ dose will also be given 1 month after Dose 1 of BNT162b2$_{SA}$.
- When given as a 2-dose series, separated by 21 days, in newly recruited participants who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19.

In addition, a group of C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously will receive a third dose of BNT162b2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

This approach will allow an evaluation of immunogenicity against the reference ancestral SARS-CoV-2 strain (Wuhan-Hu-1/USA-WA1) and the selected South African VOC, using a noninferiority approach based on neutralizing antibody titers in prior BNT162b2 vaccinees who receive either a homologous boost (with BNT162b2) or a heterologous boost (with BNT162b2$_{SA}$), as well as new vaccinees receiving 2 doses of BNT162b2$_{SA}$.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.6. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization. For the boostability and protection-against-VOCs subset (both existing and newly enrolled), male or female participants between the ages of 18 and 55 years, inclusive, at rerandomization/enrollment. Note that participants <18 years of age cannot be enrolled in the EU.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

    Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

5. **Boostability and protection-against-VOCs existing participant subset only:** Participants who provided a serum sample at Visit 3, with Visit 3 occurring within the protocol-specified window.

Informed Consent:

6. Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - Chronic liver disease

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
- Resident in a long-term facility
- BMI >30 kg/m^2
- Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry through and including 6 months after the last dose of study intervention, with the exception of interventional studies for prevention of COVID-19, which are prohibited throughout study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;
    - Sore throat;
    - Diarrhea;
    - Vomiting.
2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 3 investigational RNA vaccine candidates, with the addition of saline placebo, are the 4 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg
- BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S containing South Africa B.1.351 variant–specific mutations): 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	10-, 20-, 30-µg	30-µg	N/A

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2$_{SA}$ (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. Participants ≥16 years of age who originally received placebo and accept the offer to receive BNT162b2 at defined points as part of the study will receive 1 dose of BNT162b2 at each additional vaccination visit (Visits 101 and 102) in accordance with the study's additional SoA (Section 1.3.3). The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162 at Visit 8a.

Participants in the subset for evaluation of boostability and protection against emerging VOCs will receive either a third dose of BNT162b2 or BNT162b2$_{SA}$ approximately 5 to 7 months after their second dose of BNT162 at Visit 301. Of those who receive BNT16b2$_{SA}$ at Visit 301, a subset will receive a further dose of BNT162b2$_{SA}$ at Visit 303.

BNT162b2-naïve participants who are enrolled under protocol amendment 14 to receive BNT162b2$_{SA}$ will receive 1 dose of study intervention at each vaccination visit, Visits 401 and 402.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

9. Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

To allow administration of BNT162b2 to participants who originally received placebo, site staff will be unblinded to individual participants' original study intervention allocation as the participants become eligible for vaccination under local/national recommendations or from 6 months after the second dose.

For the group of 30 existing Phase 3 participants 18 to 55 years of age who will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the investigator will not be.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).

- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

- After the formal data release of the final efficacy analysis of at least 164 cases, which is considered the primary completion of the study efficacy objectives, additional statisticians and programmers will become unblinded at the participant level to prepare unblinded analyses and other regulatory activities. A group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study.

- After the study data used for submission become public, the blinded study team will also have access to those data, and become unblinded at a group level.

- When a participant is unblinded for potential receipt of BNT162b2 (if he or she originally received placebo) per Section 8.16, the study team will become unblinded to the participant's original study intervention allocation.

For the group of 30 existing Phase 3 participants 18 to 55 years of age who will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$, through 1 month after their first dose of

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the sponsor will not be.

The study will be unblinded in stages once all ongoing participants either have been individually unblinded or have concluded their 6-month post–Dose 2 study visit, as follows:

- Phase 1 (after Visit 8).
- Phase 2/3, ≥16 years (after Visit 4).
- Phase 3, 12 to 15 years (after Visit 4).
- Original Phase 3 participants rerandomized to assess boostability and protection against emerging VOCs (after Visit 306).

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

Instructions on how to unblind participants ahead of administration of BNT162b2 to placebo recipients, or for other, nonemergency reasons, will be provided separately: this unblinding will NOT be performed in the IRT. The date (that the participant becomes aware of study intervention allocation) and reason that the blind was broken must be recorded in the source documentation and CRF.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants). In addition, for Phase 1 participants who go on to receive a third dose of BNT162, concomitant vaccinations will be collected from the time the participant provides informed consent (for receipt of Vaccination 3) through and including Visit 8c (1 month after the third dose). For BNT162-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to the time the participant provides informed consent (for participation in the subset) through and including Visit 306. For BNT162b2-naïve participants, the subset for evaluation of protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to study enrollment through and including Visit 405.

- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 and from 28 days prior to Visit 8a to Visit 8c for Phase 1 participants, and from 28 days prior to enrollment to Visit 3 for Phase 2/3 participants). Use is also prohibited for participants in the subset for evaluation of boostability and protection against emerging VOCs, from 28 days prior to Visit 301 to Visit 303/305 and the BNT162b2-naïve participants from 28 days prior to enrollment to Visit 404.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, for whatever reason, a participant receives only 1 dose of BNT162b2, the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. For example, because of a medication error a participant receives only 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa); the participant can return at a later date for the unscheduled visit. In this situation:

- Obtain informed consent.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s).

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

If a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately up to: 500 mL for participants in Phase 1, 110 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum.

Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 670 mL during the 24-month study period.

For those Phase 3 participants enrolled in the subset to receive an additional dose of BNT162b2 or BNT162b2$_{SA}$, the total blood sampling volume for individual participants in this study is approximately up to 310 mL for those who receive 3 doses and 410 mL for those who receive 4 doses. Those participants in the subset who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of approximately up to 795 mL.

For those participants enrolled into the additional cohort (added as part of protocol amendment 14) of BNT162b2-naïve participants who will receive 2 doses of BNT162b2$_{SA}$, the total blood sampling volume for individual participants is approximately up to 250 mL. Those participants in the cohort who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of approximately up to 735 mL.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Additionally, 20 mL of blood for participants ≥16 years of age and 10 mL for participants in the 12- to 15-year age stratum will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection.

For all participants, other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

8.1.1. Efficacy Against COVID-19

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[10] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
  - Fever;
  - New or increased cough;
  - New or increased shortness of breath;

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction*;
  - Admission to an ICU;
  - Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

8.1.2. Efficacy Against Asymptomatic SARS-CoV-2 Infection

VE against asymptomatic SARS-CoV-2 infection will be evaluated in 2 ways: through impact on seroconversion of N-binding antibody and impact on NAAT-confirmed SARS-CoV-2 infection, in originally enrolled Phase 2/3 participants not suffering from COVID-19. Data from participants who receive more than 2 doses of BNT162b2 will not be included after they receive a third dose.

8.1.2.1. Seroconversion of N-Binding Antibody

Blood samples for assessment of N-binding antibodies are drawn at multiple scheduled visits. An asymptomatic case of SARS-CoV-2 infection based on seroconversion of N-binding antibody is defined as positive N-binding antibody at a post–Dose 2 visit in participants without serological evidence of infection (determined by negative N-binding antibody) at Visit 1 or virological evidence of infection (determined by negative NAAT result at Visit 1 and Visit 2 and at the time of a potential COVID-19 illness). The requirement for a negative NAAT result at Visit 2 is to focus on assessment of protection against asymptomatic infection after 2 doses of vaccine, to the extent possible in an analysis based on seroconversion of N-binding antibody, recognizing that it is not possible to identify and exclude all asymptomatic infections that occur after Dose 1 and prior to Dose 2.

A secondary definition will be applied without the requirement for a negative NAAT result at Visit 2 to allow assessment of protection after 1 dose of vaccine. A positive N-binding antibody at a postvaccination visit in participants with negative N-binding antibody at Visit 1 and negative NAAT results at Visit 1 and at the time of a potential COVID-19 illness is considered an asymptomatic case.

8.1.2.2. NAAT-Confirmed SARS-CoV-2 Infection

For participants who consent to participate in an intensive period of surveillance, nasal swabs will be obtained to assess SARS-CoV-2 infection by NAAT (see Section 8.1.5).

An asymptomatic case of NAAT-confirmed SARS-CoV-2 infection is defined as a positive NAAT result on a nasal swab collected during the surveillance period from participants without COVID-19 symptoms at the time the nasal swab was taken, or within 14 days after it. The onset date of the asymptomatic case is the collection date of the first nasal swab that tested positive.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof are expressly excluded.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

8.1.3. Vaccine-Induced Immunogenicity

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay (reference strain and SA variant)
- Full-length S-binding or S1-binding IgG level assay
- RBD-binding IgG level assay (Phase 1 only)

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

Additional whole blood samples of ~120 mL will be obtained from a group of up to approximately 30 participants in each group in the subset for evaluation of boostability and protection against emerging VOCs (both BNT162b2-experienced and BNT162b2-naïve) at select sites for isolation of PBMCs. These samples will be used to describe T-cell responses to emerging VOCs and reference strains. A blood sample of ~5 mL for HLA typing will also be obtained.

8.1.4. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

8.1.5. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emea.europa.eu

where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.6.

The nasal swabs will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2. For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with Section 8.3.2.

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Certain participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. In addition, participants 16 through 17 years of age enrolled under protocol amendment 9 and onwards will be included in the reactogenicity subset. All other participants, including those who originally received placebo and then received BNT162b2 under protocol amendment 10 and onwards, will not complete a reactogenicity e-diary but will have their local reactions and systemic events detected and reported as AEs in accordance with Section 8.3.2. Phase 1 participants who receive a third dose of BNT162b2 will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage in the reactogenicity e-diary for 7 days following administration of the study intervention. Participants in the subset for evaluation of boostability and protection against emerging VOCs (both BNT162b2-experienced and BNT162b2-naïve) will be asked to monitor and record local reactions, systemic events, and antipyretic medication use in the reactogenicity e-diary for 7 days following each administration of the study intervention.

The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[9]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the administration of the second dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.
2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.
3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.
4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Additionally, for those participants who originally received placebo but go on to receive BNT162b2 at Vaccinations 3 and 4, AEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) through and including Visit 103. SAEs will be collected from the time the participant provides informed consent

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

(for receipt of Vaccinations 3 and 4) to approximately 6 months after the second dose of BNT162b2 (Visit 104).

For Phase 1 participants who go on to receive a third dose of BNT162, AEs and SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccination 3) through and including Visit 8c (1 month after the third dose).

For BNT162b2-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, AEs will be collected from the time the participant provides informed consent (for participation in the subset) through and including Visit 303 for those receiving 1 additional dose and Visit 305 for those who receive 2 additional doses. For both schedules, this equates to collection for up to 1 month after the last dose. SAEs will be collected from the time the participant provides informed consent (for participation in the subset) through and including Visit 306 (5 or 6 months after the last dose, depending upon group).

For BNT162b2-naïve participants, the subset for evaluation of protection against emerging VOCs, AEs will be collected from the time the participant provides informed consent through and including Visit 404 (1 month after the second dose). SAEs will be collected from the time the participant provides informed consent through and including Visit 405 (6 months after the second dose).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Report Form and EDP Supplemental

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.6. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.6.1. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

8.3.7. Cardiovascular and Death Events

Not applicable.

8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.9. Adverse Events of Special Interest

Not applicable.

8.3.9.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.10. Medical Device Deficiencies

Not applicable.

8.3.11. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

Unless stated otherwise, all study visits are intended to be conducted in person at the study site. If this is not possible, because of local circumstances related to the COVID-19 pandemic, study procedures that do not require in-person participant contact may be performed by telehealth. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Irrespective of the nature of the contact, all visit procedures are expected to be performed on the same day.

As the protocol design includes visits of an unplanned nature, multiple visits may occur on the same day, but all procedures for all visits must be conducted (including collection of all blood samples).

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Fever ≥39.0°C (≥102.1°F).
- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Between Visits 8 and 9

All participants who have not already been unblinded, no later than at the approximate time participants in Phase 2/3 reach Visit 4, will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, he or she will move to the procedures in Section 8.16.

8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of a third dose of BNT162, his or her next visit should be Visit 9.

- Confirm that the participant originally received 10-µg, 20-µg, or 30-µg doses of BNT162b1 or BNT162b2 at Vaccinations 1 and 2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Record nonstudy vaccinations as described in Section 6.5.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 2, 3, and 6 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer a 30-µg dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
    - Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
    - Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):
        - Fever ≥39.0°C (≥102.1°F)
        - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)
        - Severe pain at the injection site
        - Any severe systemic event
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.

- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF and on an SAE form as applicable.
- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
    - Severe pain at the injection site.
    - Any severe systemic event.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.

- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- If Visit 3 is being conducted under amendment 12 onward: If the participant is ≥16 years of age, and is eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, determine if he/she is willing to receive BNT162b2 as part of the study. If so, unblind the participant's study intervention assignment, and move placebo recipients to the procedures in Section 8.16.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- If not already unblinded, unblind the participant's study intervention assignment, and move placebo recipients willing to receive BNT162b2 to the procedures in Section 8.16.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;

- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;

- Fever;

- New or increased cough;

- New or increased shortness of breath;

- Chills;

- New or increased muscle pain;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
  - Symptoms and signs, including
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
    - Significant acute renal, hepatic, or neurologic dysfunction

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

  - Clinical diagnosis
  - Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.
  - Full blood count
  - Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
  - Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
  - Number and type of any healthcare contact; duration of hospitalization and ICU stay
  - Death
- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

8.15. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 or 14 days after receipt of the second dose, depending on the objective) of past SARS-CoV-2 infection.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

- Asymptomatic SARS-CoV-2 infection surveillance visits: To determine the incidence of asymptomatic SARS-CoV-2 infection.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, asymptomatic SARS-CoV-2 infection surveillance visit swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result, either asymptomatic or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result), prior to Visit 2 should receive Vaccination 2 as normal.

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

If a participant ≥16 years of age becomes eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study.

Placebo recipients ≥16 years of age who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Dose 2, and will follow the procedures listed in this section for the remainder of their participation in the study. For Phase 2/3 participants, Visit 101 could occur at the same time as the original Visit 4.

8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant originally received only placebo at Vaccination 1/2. Secondary confirmation by another site staff member is required.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 4 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101)

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Record AEs as described in Section 8.3.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Review and consider inclusion criteria 2, 3, and 6 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record AEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 103 (if any).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment to call the participant by telephone for the next study contact.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 104 (if any).

- Request the return of the participant's e-diary or assist the participant/participant's parent(s)/legal guardian to remove the study application from his or her own personal device.

- Inform the participant/participant's parent(s)/legal guardian that his or her study participation has ended.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.17. Administration of an Additional Dose of BNT162b2 or BNT162b2$_{SA}$

The assessment of boostability will be further expanded in a subset of Phase 3 participants who will receive a third dose of BNT162b2 or a third and potentially a fourth dose of prototype BNT162b2$_{SA}$.

8.17.1. Visit 301 – Vaccination 3: (150 to 210 Days After Visit 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

and dated ICD addendum must be given to the participant. If the participant does not consent to administration of a third dose of BNT162b2, he or should remain on the Phase 2/3 visit schedule.

Note: This visit can occur on the same day as Visit 4, but all procedures for both visits must be conducted (including collection of all blood samples).

- Confirm that the participant originally received BNT162b2 at Vaccinations 1 and 2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Record nonstudy vaccinations as described in Section 6.5.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 1, 2, 3, 5, and 6 are met and exclusion criteria 1, 3, 5, 8, 10, 11, 12, 13, 15, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. **The IRT system will also assign an additional single participant number; this number will not be used as the primary identifier for the participant, but must be included in the participant's source documents and transcribed into the CRF**. The system will also identify those participants who are to receive a fourth dose; this should be kept blinded until from the participant until Visit 303.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

    - Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

    - Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):

        - Fever ≥39.0°C (≥102.1°F)

        - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)

        - Severe pain at the injection site

        - Any severe systemic event

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.17.2. Visit 302 – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 301)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.3. Visit 303 – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 301)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.

Only if the participant is to receive a further dose of BNT162b2$_{SA}$:

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Measure the participant's body temperature.
- Ensure and document that inclusion criteria 1, 2, 3, 5, and 6 are met and exclusion criteria 1, 3, 5, 8, 10, 11, 12, 13, 15, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):
  - Fever ≥39.0°C (≥102.1°F)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)
- Severe pain at the injection site
- Any severe systemic event

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.4. Visit 304 – 1-Week Follow-up Visit (Vaccination 4): (6 to 8 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2SA

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

8.17.5. Visit 305 – 1-Month Follow-up Visit (Vaccination 4): (28 to 35 Days After Visit 303): Only for Those Participants Who Received a fourth dose of BNT162b2$_{SA}$

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.6. Visit 306 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 301):

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record latest CD4 count and HIV viral load.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.17.7. Visit 307 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 301):

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record latest CD4 count and HIV viral load.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.18. Administration of BNT162b2$_{SA}$ to BNT162b2-naïve Participants

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

8.18.1. Visit 401 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.

    - Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

    - Provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.

- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

    - Fever ≥39.0°C (≥102.1°F).

    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

    - Severe pain at the injection site.

    - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the study intervention accountability records.

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.18.2. Visit 402 – Vaccination 2: (19 to 23 Days After Visit 401)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.

This document cannot be used to support any marketing authorisation application (ema.europa.eu)
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document and any extensions or variations thereof

- Site staff member(s) will dispense/administer 1 dose of BNT162b2$_{SA}$ into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the study intervention accountability records.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.18.3. Visit 403 – 1-Week Follow-up Visit (After Vaccination 2): (6 to 8 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.18.4. Visit 404 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.18.5. Visit 405 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 402)

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.18.6. Visit 406 – 18-Month Follow-up Visit: (532 to 560 Days After Visit 402)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.19. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11 until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The surveillance will be conducted per the procedures listed below.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

8.19.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11

Before surveillance begins and any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

The visit should be conducted only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1) and this visit should be temporarily delayed until the symptoms have resolved.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 3 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Record AEs as described in Section 8.3 (only if the participant remains in the AE reporting period; see Section 8.3.1).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Ask the participant to obtain a surveillance self-swab at home in approximately 14 days or schedule an appointment for the participant to return to collect the swab at the site. The swab should be collected only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.19.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection

This is a repeating swab collection and will be conducted approximately every 14 days until the intensive surveillance period ends.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Participant collects a self-swab and ships it to the site for assessment at the central laboratory. The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- Complete the source documents with the swab information.

- The investigator or an authorized designee completes the CRFs with the swab information.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by all-available efficacy population. Missing laboratory

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either VE_1 >30% or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated based on the lower bound of the 95% CI. VE will be demonstrated if the lower bound of the 2-sided 95% CI for VE is >20%.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

9.1.2.2.1. Hypothesis for Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2**.** If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

9.1.2.2.2. Hypotheses for Boostability and Protection Against Emerging SARS-CoV-2 VOCs

The primary and secondary objectives for boostability and protection against emerging VOCs for BNT162b2-experienced participants and BNT162b2-naïve participants will be assessed based on:

- GMRs of SARS-CoV-2 SA and/or reference strain neutralizing titers using a 2-fold noninferiority margin. Noninferiority is met if the lower limit of the alpha-adjusted CI for the GMR is >0.5.

- The difference in percentages of participants with seroresponse to SA and/or reference strain using a 10% noninferiority margin. Noninferiority is met if the lower limit of the alpha-adjusted CI for the difference in percentages of participants with seroresponse is >-10%.

9.1.2.2.2.1. Seroresponse is defined as achieving ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse. Multiplicity Control for the Boostability and Protection-Against-VOCs Objectives

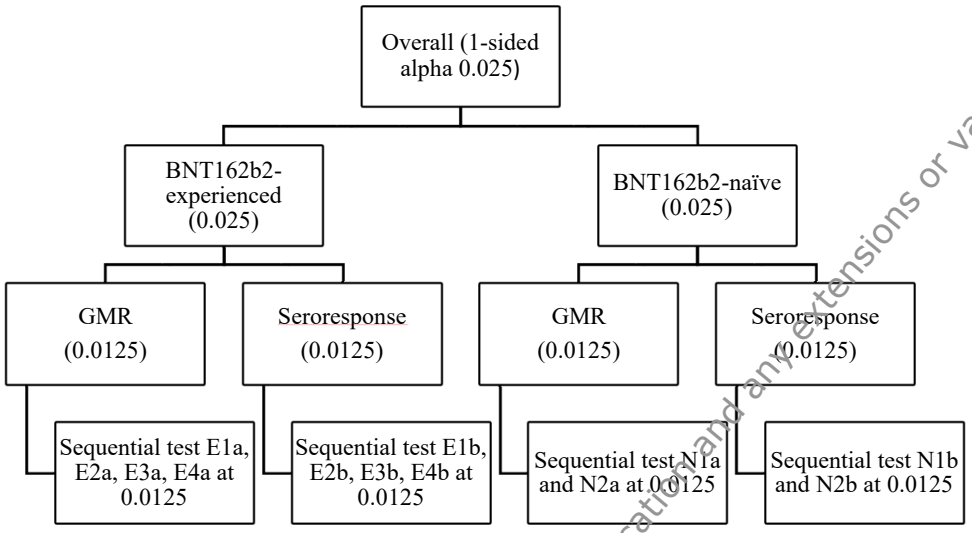
Figure 1 outlines the type I error control strategy for multiple objectives across different populations (BNT162b2-experienced or BNT162b2-naïve) and estimands (GMR or seroresponse).

The objectives for BNT162b2-experienced participants and BNT162b2-naïve participants will be evaluated independently. The vaccine-experienced and -naïve individuals are different populations with different objectives. The 2 populations are included in the same study to improve operational efficiency. Therefore, no type I error adjustments will be applied to the assessments of the 2 populations.

For each population, the objectives will be evaluated separately for each estimand. To control the overall type I error, the 1-sided alpha of 0.025 will be split and allocated equally to each estimand. Specifically, for each estimand, the hypotheses will be tested in sequential order (as listed in the objectives in Section 3) using a 1-sided alpha of 0.0125 (Figure 1, where E and N represent vaccine-experienced and vaccine-naïve, respectively, and a and b represent GMR and seroresponse estimands, respectively).

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Figure 1. Multiplicity Schema



9.2. Sample Size Determination

9.2.1. Phase 1

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

9.2.2. Efficacy Against COVID-19

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

9.2.3. Efficacy Against Asymptomatic Infection

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection will be assessed in Phase 2/3 participants (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT). Assuming a true VE of 70%, a total of 53 asymptomatic cases will provide approximately 90% power to conclude true VE >20%. A total of 206 cases is needed to have 90% power if the true VE is 50%. The hypothesis for asymptomatic seroconversion of N-binding antibody will be tested if at least 206 cases are accrued. The hypothesis for asymptomatic infection based on central laboratory–confirmed NAAT in participants who are consented to participate in the intensive surveillance phase will be tested if at least 53 cases are accrued.

9.2.4. Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 280 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.65	-0.2	225	90.4%

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer.
a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).
b. At 0.05 alpha level (2-sided).

9.2.5. Boostability and Protection Against Emerging SARS-CoV-2 VOCs

To assess boostability and protection against emerging SARS-CoV-2 VOCs, approximately 300 participants will be enrolled in each of the 3 groups (BNT162b2-experienced participants to receive either a third dose of BNT162b2 [Group 1] or a third dose of BNT162b2$_{SA}$ [Group 2], BNT162b2-naïve participants to receive 2 doses of BNT162b2$_{SA}$ [Group 3]) to provide an acceptable safety database.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Assuming 20% nonevaluable rate, approximately 240 evaluable participants in each group will contribute to immunogenicity evaluation. This will provide sufficient power for noninferiority evaluations with appropriate multiplicity adjustment for type I error control.

For comparisons based on GMR, the assay standard deviation in log scale is assumed to be 0.74 based on results from Phase 2 of the study and adjusted for assay variability. A GMR of 1 is assumed for each comparison.

For comparisons based on seroresponse, a 90% response rate is assumed for each comparative group or at each comparative time point.

Within-Group Comparison for BNT162b2-Experienced Participants

For each randomized group of BNT162b2-experienced participants (Group 1: received a third dose of BNT162b2 and Group 2: received a third dose of BNT162b2$_{SA}$), with 240 evaluable participants and the stated assumptions for the GMR and standard deviation, the study has >99.9% power to demonstrate NI based on GMR for the objectives in vaccine-experienced individuals using a 2-fold margin.

Assuming true response rate of 90% in each group, the study has 89.7% power to show NI based on seroresponse rate for the objectives in vaccine-experienced individuals using a 10% margin.

Between-Group Comparison of BNT162b2-Naïve Participants to Selected Existing Phase 3 Participants Who Received 2 Doses of BNT162b2

Approximately 300 participants will be randomly selected from the existing Phase 3 participants who received 2 doses of BNT162b2 to form the control group for the BNT162b2-naïve participants. The selection will ensure comparable distribution of age, sex, and other demographic factors in the control group and BNT162b2-naïve group. With 240 evaluable BNT162b2-naïve participants and 240 evaluable participants in the control group and the above stated assumptions for the GMR, standard deviation, and seroresponse rate, the study has >99.9%% power to declare NI based on GMR for the objectives in vaccine-naïve individuals using a 2-fold margin and 89.7% power to declare NI based on seroresponse rate using a 10% margin.

9.2.6. Safety

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=300	N=1000	N=3000	N=6000	N=9000	N=10000
0.01%	0.00	0.00	0.02	0.03	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.06	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.11	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.16	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.21	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.26	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.36	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.45	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.53	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.59	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.65	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.78	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	0.95	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 3 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 as initially randomized, with Dose 2 received within the predefined window, receive a third dose of BNT162b2 or $BNT162b2_{SA}$ as rerandomized, have at least 1 valid and determinate immunogenicity result after Dose 3 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 4 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 as initially randomized, with Dose 2 received within the predefined window, receive 2 booster doses of $BNT162b2_{SA}$ as rerandomized, have at least 1 valid and determinate immunogenicity result after Dose 4 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Population	Description
Dose 3 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 at initial randomization, receive a third dose of BNT162b2 or BNT162b2$_{SA}$ at rerandomization, and have at least 1 valid and determinate immunogenicity result after Dose 3.
Dose 4 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 at initial randomization, receive 2 booster doses of BNT162b2$_{SA}$ at rerandomization, and have at least 1 valid and determinate immunogenicity result after Dose 4.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
Evaluable efficacy (seroconversion)	All eligible randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window, have at least 1 N-binding antibody test result available at a post-Dose 2 visit, and have no other important protocol deviations as determined by the clinician prior to Dose 2.
Evaluable efficacy (asymptomatic surveillance)	All eligible randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window, consent to participate in the asymptomatic surveillance, and have no other important protocol deviations as determined by the clinician on or before the start of the asymptomatic surveillance period.
All-available efficacy	Dose 1 all-available: All randomized participants who receive at least 1 vaccination. Dose 2 all-available: All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention. Analyses of reactogenicity endpoints will be based on a subset of the safety population that includes participants with any e-diary data reported after vaccination.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Empirical RCDCs will be provided for all immunogenicity analyses.

Endpoint	Statistical Analysis Methods
Primary immunogenicity (Phase 3, boostability and protection against emerging VOCs)	In order to allow direct comparability with the reference strain, the anti-SA NTs may be adjusted to account for intrinsic variant or assay characteristics. The small group of existing Phase 3 participants who are to receive a third and fourth dose of BNT162b2$_{SA}$ will not be included in the primary and secondary analyses except for the last secondary descriptive objective. ***<u>BNT162b2-Experienced Participants:</u>*** **E1a: GMR of reference strain NT 1 month after the third dose of BNT162b2 to 1 month after the second dose of BNT162b2 in the same individuals** **E2a: GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** The comparisons of different NTs (anti-SA or anti–reference strain) or the same NTs at different time points within the same group will be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
	limited to participants with nonmissing values at both time points or both NT measurements. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (eg, later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 97.5% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. Noninferiority of E1a and E2a will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.5. **E1b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 and 1 month after the second dose of BNT162b2 in the same individuals** **E2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** The percentages of participants with seroresponse at each time point and the difference in percentages will be provided. The 2-sided 97.5% CIs for the difference in percentages of participants with seroresponse will be calculated using the Miettinen and Nurminen method. Noninferiority of E1b and E2b will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%. ***BNT162b2-Naïve Participants:*** **N1a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2** For the between-group comparison, GMRs will be calculated as the mean of the difference of logarithmically transformed assay results between 2 groups and exponentiating the mean. The associated 2-sided 97.5% CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed titers and exponentiating the confidence limits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
	Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.5. **N1b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2** The difference in percentages of participants with seroresponse and associated 2-sided 97.5% CIs will be calculated in the same way as for primary endpoints E1b and E2b. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%.
Secondary immunogenicity (Phase 3, boostability and protection against emerging VOCs)	***BNT162b2-Experienced Participants:*** **E3a: GMR of SA NT 1 month after the third dose of BNT162b2 to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** **E4a: GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 in the same individuals** **E3b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** **E4b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2 in the same individuals** GMRs and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1a and E2a. If noninferiority of E1a and E2a are both established, E3a and E4a will be assessed sequentially using the same criterion (lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.5).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
	The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. Similarly, if noninferiority of E1b and E2b are both established, E3b and E4b will be assessed sequentially using the same criterion (lower bound of the 2-sided 95% CI for the difference in percentages is greater than -10%). **GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2** **The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. **GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals** **The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint E1a and E2a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. ***BNT162b2-Naïve Participants:*** **N2a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2**

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	N2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2 GMR and the associated 2-sided 97.5% CI will be calculated in the same way as for the primary endpoint N1a. Statistical superiority of N2a will be assessed if noninferiority of N1a is established. Superiority of N2a will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 1. The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1b and E2b. Statistical superiority of N2b will be assessed if noninferiority of N1b is established. Superiority of N2b will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than 0%. **GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2** **The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2** GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints E1b and E2b
Secondary immunogenicity (Phase 1)	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
	• Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
	GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the 16- to 25-year age group)	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and 2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment. The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years

This document can only be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
	minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2: **GMTs/GMCs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level** GMTs/GMCs and 2-sided 95% CIs will be provided by initial vaccine and age group for the following time points: • At Dose 3 and 7 days and 1 month after Dose 3 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level** GMFRs from Dose 3 to 7 days and 1 month after Dose 3 and 2-sided 95% CIs will be provided by initial vaccine and age group. GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
	GMRs of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2 GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed reference-strain titers for each participant (1 month after Dose 3 – 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. **GMRs of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2** GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (SA-variant titer at 1 month after Dose 3 – reference-strain titer at 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.
Exploratory immunogenicity (Phase 2/3)	**GMTs/GMCs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers,

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
	calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels after Dose 1 and after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
Exploratory immunogenicity (Phase 3, boostability and protection against emerging VOCs)	**Geometric mean NT for any VOC not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2** Geometric means and associated 2-sided 95% CIs of any anti-VOC neutralizing titers will be provided at each time point for each group.

9.4.2. Efficacy Analyses

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
	vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.
Secondary	**First: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Second: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Third and fourth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Fifth and sixth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
	The following secondary efficacy endpoints for COVID-19 illness according to CDC-defined symptoms will be evaluated descriptively with 95% CIs. **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days or from 14 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[10] Missing efficacy data will not be imputed. The following secondary efficacy endpoints regarding asymptomatic SARS-CoV-2 infection will be evaluated based on a success criterion of the lower bound of the 2-sided 95% CI for VE being >20%. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate per 1000 person-years of follow-up in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The hypothesis will be tested if at least 206 cases are accrued. In addition, a descriptive summary of VE against asymptomatic infection over different time intervals (ie, prior to 1 month after

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
	Dose 2, from 1 month after Dose 2 onward), along with the associated 2-sided 95% CI, will be calculated using the same method. The analysis of the primary definition of asymptomatic cases will be based on the evaluable efficacy (seroconversion) population and the Dose 2 all-available efficacy population. The analysis of the secondary definition of asymptomatic cases will be based on the Dose 1 all-available efficacy population. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants without evidence of infection (up to the start of asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The hypothesis will be tested if at least 53 cases are accrued. The analysis will be based on the evaluable efficacy (asymptomatic surveillance) population and the all-available efficacy population and will include only participants who are consented to participate in the asymptomatic surveillance and who do not have serological or virological evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period.
Exploratory	**Ratios of confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants without, and with and without, evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** After the primary objectives are met at the final analysis of at least 164 first primary cases, the study will continue with blinded follow-up until the participant is unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. A descriptive update of VE will be provided with additional follow-up data. VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness from 7 days after the second dose through the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
	blinded follow-up period. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[10] Supportive analysis of time to confirmed COVID-19 illness will be performed using Kaplan-Meier cumulative incidence curves. Participants who were randomized to placebo will be censored at the time of receipt of BNT162b2. **Incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness from 7 days after the second dose will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted. **Incidence of asymptomatic SARS-CoV-2 infection through the entire study follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants who received BNT162b2 and who have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for asymptomatic infection will be provided for participants who received BNT162b2 at initial randomization and have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with evidence of infection (up to the start of the asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. Participants who are consented to participate in the asymptomatic surveillance and who have serological or virologic evidence of past

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
	SARS-CoV-2 infection up to the start of the asymptomatic surveillance period will be included in the analysis.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[11] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
	Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group. AEs and SAEs reported during the open-label follow-up period will be summarized separately for participants who were unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. For Phase 3 participants enrolled for assessment of boostability and protection against emerging VOCs, descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for local reactions and systemic events from Day 1 through Day 7 after each dose, AEs from Dose 1 to 1 month after the last dose, and SAEs from Dose 1 to 5 or 6 months after the last dose. Local reactions and systemic events from Day 1 through Day 7 after each dose will be presented by severity and cumulatively across severity levels. The safety analyses are based on the safety population. Analyses of reactogenicity endpoints are based on a subset of the safety population that includes participants with any e-diary data reported after vaccination. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2: Descriptive statistics will be provided by initial vaccine and age group for local reactions and systemic events from Day 1 through Day 7 after Dose 3, and AEs/SAEs from Dose 3 to 1 month after Dose 3. Local reactions and systemic events from Day 1 through Day 7 after Dose 3 will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Endpoint	Statistical Analysis Methods
	percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs.

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" and each lot of "Process 2" will be summarized descriptively. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected randomly for the analysis.

Exploratory analyses to investigate possible immunological correlates with efficacy, and characterization of infecting SARS-CoV-2 variants, may be conducted.

The cell-mediated immune response and additional humoral immune response parameters to the reference strain and SA will be summarized for the subset of participants with PBMC samples collected.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive PPOS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 6 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu/contact

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8, for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

Only the first primary endpoint will be analyzed at IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints (confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and in all

This document cannot be used to support any marketing authorisation application on ema.europa.eu and any extensions or variations thereof

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

participants, confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection and in all participants) will be evaluated sequentially in the stated order, by the same method used for the evaluation of primary VE endpoints. Success thresholds for secondary VE endpoints will be appropriately chosen to control overall type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Complete safety and immunogenicity analysis approximately 1 month after Dose 3 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data (with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.
- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.
- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.
- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2.
- Complete safety and immunogenicity analysis approximately 1 month after Dose 3 for Phase 3 participants included in the booster evaluation and approximately 1 month after Dose 2 for newly enrolled Phase 3 participants included in the BNT162b2$_{SA}$ evaluation.
- Analysis of efficacy against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) when a sufficient number of cases have accrued to evaluate the objective(s).

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Complete safety and efficacy analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.

- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort

- Review of safety data in the case of a stopping rule being met

- Review of safety and/or immunogenicity data to:

  - Allow groups of participants of 65 to 85 years of age to proceed

  - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review

- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:

  - Whether any groups may not be started

  - Whether any groups may be terminated early

  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses

- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule

- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Up until the final efficacy analysis, 3 blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial. When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
E1, E2, etc	vaccine-experienced (statistical tests)
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Abbreviation	Term
LNP	lipid nanoparticle
LPX	lipoplex
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N1, N2, etc	vaccine-naïve (statistical tests)
N/A	not applicable
NAAT	nucleic acid amplification test
NI	noninferiority
non-S	nonspike protein
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SA	South Africa
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Abbreviation	Term
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
UK	United Kingdom
ULN	upper limit of normal
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
VOC	variant of concern
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs after accrual of at least 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.

4 Centers for Disease Control and Prevention. Emerging SARS-CoV-2 variants. Available from: https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html. Updated: 28 Jan 2021. Accessed: 10 Feb 2021.

5 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

6 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

7 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

8 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

9 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

10 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

11 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 14, Clean Copy, 02Mar2021
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	02-Mar-2021 14:05:54	Business Line Approver
PPD	02-Mar-2021 14:41:12	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19668af9a\Approved\Approved On: 02-Mar-2021 14:41 (GMT)

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**

Protocol amendment 13	12 February 2021	• In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2:
		  • Added corresponding objectives, estimands, and endpoints
		  • Added corresponding SoA and procedures
		  • Added details in the statistical methods sections.
		• Clarified the population used for analysis of reactogenicity endpoints.
		• To align with current recommendations, investigators may exercise judgment on review of inclusion and exclusion criteria ahead of vaccination with BNT162b2 for participants who originally received placebo.
		• Clarified that if a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent.
		• Participants who provide biweekly swabs for surveillance of asymptomatic infection should now continue to swab even after unblinding if they originally received BNT162b2, to maximize the numbers of swabs to be collected.
		• Clarified the procedures for unscheduled visits to administer a second dose in the event a participant received only 1 dose of BNT162b2.

Protocol amendment 12	14 January 2021	• Because of a formatting error in protocol amendment 11, exclusion criterion 4 was inadvertently added to exclusion criterion 3 and the subsequent criteria renumbered. This amendment corrects that error. • Because of a change in the pace with which participants ≥16 years of age who originally received placebo will become eligible for receipt of BNT162b2, text was updated throughout the protocol to reflect that this will happen in a phased manner, with recommendations detailed separately and available in the electronic study reference portal. • Clarified that participants who are unblinded because they become potentially eligible for

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		receipt of BNT162b2 will not participate in surveillance for asymptomatic SARS CoV-2 infection. • Corrected the exploratory objective to describe non-S seroconversion to SARS-CoV-2 to clarify that this will only include participants who received BNT162b2 at initial randomization (since those who received it subsequently do not have blood drawn). • In line with current recommendations, removed the requirement to discontinue study intervention because of a diagnosis of COVID-19 during the study.

Protocol amendment 11	04 January 2021	• Added approaches to evaluate efficacy against asymptomatic SARS-CoV-2 infection:
		  • Added objectives, estimands, and endpoints, and statistical methods, for assessment via N-binding antibody seroconversion;
		  • Added a potential intensive surveillance period for nasal swabbing, for assessment via NAAT:
		  • Corresponding objectives, estimands, and endpoints added
		  • Corresponding SoA and procedures added
		  • Details added in the statistical methods sections.
		• Added the possibility of assessing full-length S-binding, instead of S1-binding, IgG levels in Phase 2/3.
		• Clarified in Section 4.1.1 that any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity at the approximate time participants in Phase 2/3 reach Visit 4, for consistency with other sections.
		• Added a sentence to reflect that assent is obtained from participants <18 years of age.

Protocol amendment 10	01 December 2020	• Added the possibility of administering BNT162b2 to participants who originally received placebo, following any local or national recommendations. • Added the possibility of administering BNT162b2 to participants who originally received placebo, following completion of the active safety surveillance period. • Added corresponding exploratory objectives and statistical analysis details.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Removed immunogenicity analyses of titers greater than defined threshold(s). • Removed the need for blinded COVID-19 case review after the final efficacy analysis. • Included the possibility, due to local circumstances related to the COVID-19 pandemic, that study procedures that do not require in-person participant contact may be performed by telehealth. • In light of additional information to better estimate the standard deviation of SARS-CoV-2 neutralizing titers, increased the sample size for the noninferiority immunogenicity analysis in adolescents 12 to 15 years of age.
Protocol amendment 9	29 October 2020	• To better align with the natural history of SARS-CoV-2 infection, added Phase 2/3 secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days after the second dose; also modified the existing secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days, as well as 7 days, after the second dose; • Made corresponding changes to the study design, study assessments and procedures, and statistical analysis sections. • For operational reasons, removed the interim analysis planned after accrual of 32 cases. • Clarified that interim analyses will be conducted after accrual of *at least* 62, 92, and 120 cases. • Included any participants 16 through 17 years of age enrolled under this amendment in the reactogenicity subset. • Added an unblinded clinical scientist to support DMC activities. • Clarified that serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.
Protocol amendment 8	15 October 2020	• Removed “N-binding antibody” and “SARS-CoV-2 detection by NAAT” as endpoints from the third exploratory objective, as these results are used for the determination of the population, and are not endpoints. • Clarified that the “Process 1” participants included in the descriptive analysis of “Process 1”- and “Process 2”-manufactured study interventions will be selected randomly.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified that surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study. • Further modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Clarified that for participants who are not in the reactogenicity subset, local reactions and systemic events following vaccination should be detected and reported as AEs. • Clarified that premenarchal females are not WOCBP. • Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2. • Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2." • Clarified the degree of unblinding on the unblinded submissions team in Section 6.3.3. • Made provision for a second dose of BNT162b2 in participants who were affected by a medication error at Visit 2 in Section 6.6. • Provided further clarification regarding discontinuation of study intervention in Section 7.1. • Modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Added that 2 periods of potential COVID-19 symptoms within 4 days will be considered as a single illness. • Provided guidance in Section 8.13 regarding circumstances in which a SARS-CoV-2 test might be required even if symptoms within 7 days following each vaccination are considered more likely due to vaccine reactogenicity.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Made allowance in Section 8.13 for a second SARS-CoV-2 test to be performed within the same potential COVID-19 illness if it is in accordance with routine practice. • Added Section 8.15 to describe the reporting of SARS-CoV-2 test results and their implications for participants receiving a second vaccine dose. • Added statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age. • Amended scope of analyses of safety data in Section 9.3.1. • Made various editorial changes.
Protocol amendment 6 (Germany-specific)	23 September 2020	• According to regulatory request, inclusion criterion 1 now specifies that participants less than 18 years of age will not be enrolled in the EU.
Protocol amendment 6	08 September 2020	• Reordered some procedures in the Phase 2/3 schedule of activities for consistency with the main body of the protocol. • Corrected the window for the 6-month follow-up visit to be approximately 6 months after Vaccination 2. • Reduced the volume of blood draws to ~20 mL. • Removed the need to have safety data reported for participants to be included in the safety objective assessment. • Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease. • Increased the sample size for Phase 2/3 to ~43,998. • Clarified that inclusion criterion 4 (ie, participants at higher risk for acquiring COVID-19) is applicable for Phase 2/3 only, and provided some examples. • Removed exclusion criterion 2 (ie, known infection with HIV, HCV, or HBV) for Phase 3 and added criteria for HIV-positive participants. • Decreased the lower age limit and removed the upper age limit for inclusion in Phase 2/3 in order to evaluate BNT162b2 30 µg in older adolescents and those over 85 years of age; updated the title and other references to adults to align with this change. • Renamed the immunological assays to align with other program-level documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Removed reference to the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) being "heads up." • Clarified that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention. • Added clarification that potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. • Updated the analysis population descriptions to align with the study SAP.
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory. • Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7. • Updated the stopping and alert rule parameters for enhanced COVID-19.
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation, and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol. • To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial • Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 18
1. PROTOCOL SUMMARY 20
1.1. Synopsis 20
1.2. Schema 30
1.3. Schedule of Activities 31
1.3.1. Phase 1 31
1.3.2. Phase 2/3 38
1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo 42
1.3.4. Surveillance for Asymptomatic SARS-CoV-2 Infection 44
2. INTRODUCTION 45
2.1. Study Rationale 45
2.2. Background 45
2.2.1. Clinical Overview 46
2.3. Benefit/Risk Assessment 46
2.3.1. Risk Assessment 48
2.3.2. Benefit Assessment 50
2.3.3. Overall Benefit/Risk Conclusion 50
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 50
3.1. For Phase 1 50
3.2. For Phase 2/3 52
4. STUDY DESIGN 56
4.1. Overall Design 56
4.1.1. Phase 1 57
4.1.2. Phase 2/3 58
4.2. Scientific Rationale for Study Design 60
4.3. Justification for Dose 61
4.4. End of Study Definition 61
5. STUDY POPULATION 62
5.1. Inclusion Criteria 62
5.2. Exclusion Criteria 63

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

5.3. Lifestyle Considerations 65
5.3.1. Contraception 65
5.4. Screen Failures 65
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 66
6. STUDY INTERVENTION 67
6.1. Study Intervention(s) Administered 67
6.1.1. Manufacturing Process 68
6.1.2. Administration 68
6.2. Preparation/Handling/Storage/Accountability 69
6.2.1. Preparation and Dispensing 70
6.3. Measures to Minimize Bias: Randomization and Blinding 70
6.3.1. Allocation to Study Intervention 70
6.3.2. Blinding of Site Personnel 71
6.3.3. Blinding of the Sponsor 71
6.3.4. Breaking the Blind 72
6.4. Study Intervention Compliance 72
6.5. Concomitant Therapy 73
6.5.1. Prohibited During the Study 73
6.5.2. Permitted During the Study 74
6.6. Dose Modification 74
6.7. Intervention After the End of the Study 75
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 75
7.1. Discontinuation of Study Intervention 75
7.2. Participant Discontinuation/Withdrawal From the Study 75
7.2.1. Withdrawal of Consent 76
7.3. Lost to Follow-up 77
8. STUDY ASSESSMENTS AND PROCEDURES 77
8.1. Efficacy and/or Immunogenicity Assessments 78
8.1.1. Biological Samples 81
8.1.2. Surveillance for Asymptomatic SARS-CoV-2 Infection 81

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

8.2. Safety Assessments 81
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 82
8.2.2. Electronic Diary 83
8.2.2.1. Grading Scales 83
8.2.2.2. Local Reactions 83
8.2.2.3. Systemic Events 84
8.2.2.4. Fever 85
8.2.2.5. Antipyretic Medication 86
8.2.3. Phase 1 Stopping Rules 86
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 87
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 88
8.2.6. Pregnancy Testing 88
8.3. Adverse Events and Serious Adverse Events 88
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 89
8.3.1.1. Reporting SAEs to Pfizer Safety 90
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 90
8.3.2. Method of Detecting AEs and SAEs 90
8.3.3. Follow-up of AEs and SAEs 90
8.3.4. Regulatory Reporting Requirements for SAEs 91
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 91
8.3.5.1. Exposure During Pregnancy 91
8.3.6. Exposure During Breastfeeding 93
8.3.6.1. Occupational Exposure 93
8.3.7. Cardiovascular and Death Events 93
8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 94
8.3.9. Adverse Events of Special Interest 94
8.3.9.1. Lack of Efficacy 94
8.3.10. Medical Device Deficiencies 94
8.3.11. Medication Errors 94

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.4. Treatment of Overdose 95
8.5. Pharmacokinetics 96
8.6. Pharmacodynamics 96
8.7. Genetics 96
8.8. Biomarkers 96
8.9. Immunogenicity Assessments 96
8.10. Health Economics 96
8.11. Study Procedures 96
8.11.1. Phase 1 97
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 97
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 98
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 100
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 101
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 102
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 104
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 106
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 107
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4) 107
8.11.1.10. Between Visits 8 and 9 108
8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2) 108
8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a) 110
8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a) 111
8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2 111

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2 112
8.11.2. Phase 2/3 112
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 112
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 115
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2) 117
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2) 118
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 118
8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 119
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 120
8.13. COVID-19 Surveillance (All Participants) 121
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 122
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit) 123
8.14. Communication and Use of Technology 124
8.15. SARS-CoV-2 NAAT Results 124
8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo 125
8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2) 125
8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101) 127
8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102) 128
8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102) 128

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102) 129
8.17. Surveillance for Asymptomatic SARS-CoV-2 Infection 129
8.17.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11 130
8.17.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection 131
9. STATISTICAL CONSIDERATIONS 131
9.1. Estimands and Statistical Hypotheses 131
9.1.1. Estimands 131
9.1.2. Statistical Hypotheses 132
9.1.2.1. Statistical Hypothesis Evaluation for Efficacy 132
9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity 132
9.2. Sample Size Determination 133
9.3. Analysis Sets 135
9.4. Statistical Analyses 136
9.4.1. Immunogenicity Analyses 136
9.4.2. Efficacy Analyses 141
9.4.3. Safety Analyses 146
9.4.4. Other Analyses 148
9.5. Interim Analyses 149
9.5.1. Analysis Timing 151
9.6. Data Monitoring Committee or Other Independent Oversight Committee 152
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 154
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 154
10.1.1. Regulatory and Ethical Considerations 154
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 154
10.1.2. Informed Consent Process 155
10.1.3. Data Protection 156
10.1.4. Dissemination of Clinical Study Data 156

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

10.1.5. Data Quality Assurance 157
10.1.6. Source Documents 159
10.1.7. Study and Site Start and Closure 159
10.1.8. Sponsor's Qualified Medical Personnel 160
10.2. Appendix 2: Clinical Laboratory Tests 161
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 163
10.3.1. Definition of AE 163
10.3.2. Definition of SAE 164
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 166
10.3.4. Reporting of SAEs 169
10.4. Appendix 4: Contraceptive Guidance 170
10.4.1. Male Participant Reproductive Inclusion Criteria 170
10.4.2. Female Participant Reproductive Inclusion Criteria 170
10.4.3. Woman of Childbearing Potential 171
10.4.4. Contraception Methods 172
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 174
10.6. Appendix 6: Abbreviations 176
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 180
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection 183
11. REFERENCES 184

LIST OF TABLES

Table 1. Local Reaction Grading Scale 84
Table 2. Systemic Event Grading Scale 85
Table 3. Scale for Fever 86
Table 4. Power Analysis for Noninferiority Assessment 134
Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 134
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility 150
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses 150

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall 151
Table 9. Laboratory Abnormality Grading Scale 161
Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 181
Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 182

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and efficacy of these prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	• GMC/GMT and GMFR at the time of Dose 3 and 7 days and 1 month after Dose 3. • GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2 • GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2.	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof are europa.eu

Objectives[a]	Estimands	Endpoints
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19 prior to 1 month after receipt of the second dose	In participants complying with the key protocol criteria (evaluable participants) 1 month after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 prior to 1 month after receipt of the second dose
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the efficacy of prophylactic BNT162b2 against non-Seroconversion to SARS-CoV-2 through the blinded follow-up period in participants without evidence of infection or confirmed COVID-19 during the study	In participants complying with the key protocol criteria (evaluable participants) 6 months after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization	In participants who received BNT162b2 at initial randomization 6, 12, and 24 months after receipt of the second dose of study intervention: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for a description of the manufacturing process.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

This document can be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants ≥16 years of age who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity.

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162.

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated. VE will be demonstrated if the lower bound of the 95% CI for VE is >20%.

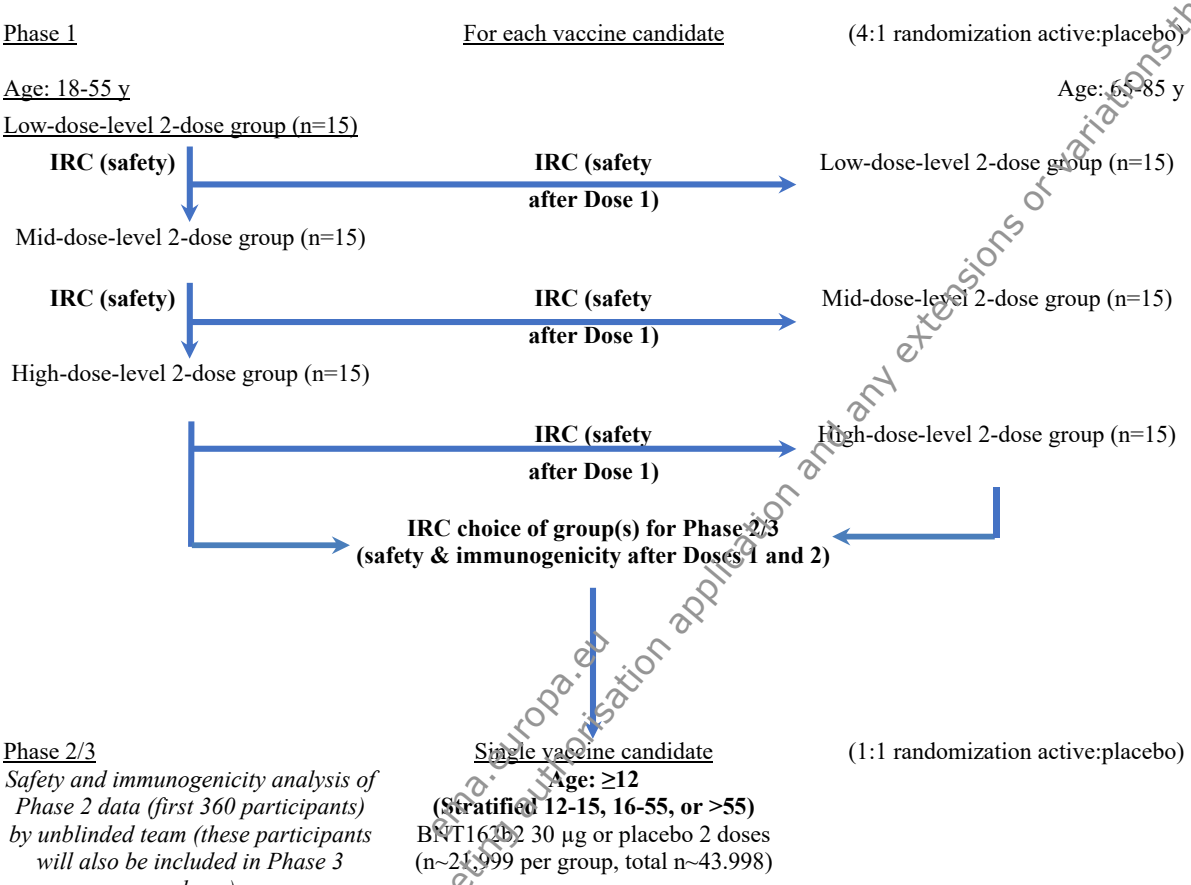
In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

Except for the objective to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age, the other immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 neutralizing titers, full-length S-binding or S1-binding IgG levels, and/or RBD-binding IgG levels (Phase 1 only) at the various time points.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

1.2. Schema



Abbreviation: IRC = internal review committee.

Note: Participants ⩾16 years of age who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b1 or BNT162b2 (at any dose level) will continue in the study as originally planned.

All other participants will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study no later than at the approximate time participants in Phase 2/3 reach Visit 4. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X								*Continued on table below*		
Assign participant number	X										
Obtain demography and medical history data	X										
Obtain details of medications currently taken	X										
Perform physical examination	X	X	X	X	X	X	X				
Measure vital signs (including body temperature)	X	X	X	X	X	X	X				
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL					
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL										
Serological test for prior COVID-19 infection	~20 mL										
Perform urine pregnancy test (if appropriate)	X	X			X						
Obtain nasal (midturbinate) swab(s)[c]		X			X					X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X			
Confirm eligibility	X	X			X						
Collect prohibited medication use			X	X	X	X	X	X		X	X

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Review hematology and chemistry results		X		X	X	X	X		*Continued on table below*		
Review temporary delay criteria		X			X						
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X			
Obtain randomization number and study intervention allocation		X									
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL			~20 mL
Administer study intervention		X			X						
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X									
Provide thermometer and measuring device		X			X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►		◄	——	►			

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	*Study procedures for Visit 8 onwards continue on the next table*	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**		**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**		**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X		*Continued on table below*		
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X		X	X
Collect e-diary or assist the participant to delete application											
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)										X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg **Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9**			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**			
Obtain informed consent		X						
Confirm participant originally received 10 to 30 µg of BNT162b1 or BNT162b2		X						
Perform urine pregnancy test (if appropriate)		X						
Confirm use of contraceptives (if appropriate)		X	X	X				
Collect prohibited medication use	X	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X				
Measure body temperature		X						
Confirm eligibility		X						
Review temporary delay criteria		X						
Collect blood sample for immunogenicity assessment	~20 mL	~20 mL	~20 mL	~20 mL	~20 mL	~20 mL		~20 mL

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg **Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9**			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**			
Obtain nasal (midturbinate) swab(s)		X					X	
Obtain the participant's vaccine vial allocation using the IRT system		X						
Administer 30-µg dose of BNT162b2		X						
Assess acute reactions for at least 30 minutes after study intervention administration		X						
Provide thermometer and measuring device		X						
Remind participant of e-diary technologies		X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		←	→					

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation applications and any extensions or variations thereof
ema.europa.eu

Continuation of table above

Visit Number	8	8a	8b	8c	9	10	Unplanned	Unplanned
Visit Description	**6-Month Follow-up Visit**	**Vax 3**	**1-Week Follow-up Visit (After Vax 3)**	**1-Month Follow-up Visit (After Vax 3)**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**175 to 189 Days After Visit 4**	**175 to 315 Days After Visit 4**	**6 to 8 Days After Visit 8a**	**28 to 35 Days After Visit 8a**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
		ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 at 10 µg, 20 µg, or 30 µg **Those participants who decline to receive a third dose of BNT162 move directly from Visit 8 to Visit 9**			**ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2 (ie, those participants who <u>do not</u> transition from placebo to BNT162b2)**			
Review ongoing reactogenicity e-diary symptoms and obtain stop dates				X				
Collect AEs and SAEs as appropriate	X	X	X	X	X[b]	X[b]	X	X
Collect e-diary or assist the participant to delete application						X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: IRT = interactive response technology; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

This document cannot be used to support any marketing authorisation applications and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant ≥16 years of age becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b2 or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b2 will continue in the study as originally planned.

All other participants ≥16 years of age who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4). If they want to receive BNT162b2, they will be unblinded and those who did originally receive placebo will move to the SoA in Section 1.3.3 for their remaining visits.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X		
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL		~20 mL/ ~10 mL
Obtain nasal (midturbinate) swab	X	X					X	
Obtain randomization number and study intervention allocation	X							
Administer study intervention	X	X						

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	◄►	◄►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X	X[f]
According to eligibility, ascertain willingness to receive BNT162b2 if originally received placebo; if willing, unblind the participant's study intervention assignment (if not already done), and move placebo recipients to the SoA in Section 1.3.3			X ◄►	X				
Collect e-diary or assist the participant to delete application						X		

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	Vaccination 1	Vaccination 2	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit[a]	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Day 1[b]	19 to 23 Days After Visit 1	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	350 to 378 Days After Visit 2	714 to 742 Days After Visit 2	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants ≥16 years of age who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. Any placebo recipient ≥16 years of age who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2.

Visit Number	101	102	103	104	105	Unplanned	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm participant meets local/national recommending criteria or is at least 175 days after Vaccination 2 (Visit 4/Visit 2)	X						
Obtain informed consent	X						
Confirm participant originally received placebo	X						
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X					
Collect prohibited medication use	X	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X		
Review and consider eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment	~20 mL						~20 mL
Obtain nasal (midturbinate) swab	X	X				X	
Obtain vaccine vial allocation via IRT	X	X					
Administer BNT162b2	X	X					

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	101	102	103	104	105	Unplanned	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Collect AEs and SAEs as appropriate	X	X	X	X		X[d]	X[d]
Contact the participant by telephone			X	X	X		
Request the participant return the e-diary or assist the participant to delete the application					X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)						X	X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

a. For participants who become eligible according to recommendations detailed separately and available in the electronic study reference portal.
b. For any remaining Phase 2/3 placebo recipients who wish to receive BNT162b2; may be combined with Visit 4 for Phase 2/3 participants.
c. Only if the participant has no blood sample collected in the previous 7 days.
d. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.4. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4 or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection.

Visit Number	201	202 Onward
Visit Description	**Asymptomatic SARS-CoV-2 Infection Surveillance Consent**	**Asymptomatic SARS-CoV-2 Infection Surveillance Swab**
Visit Window (Days)	**From Approval of Protocol Amendment 11**	**Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection**
Obtain informed consent for asymptomatic SARS-CoV-2 infection surveillance	X	
Collect prohibited medication use	X	
Collect blood sample for immunogenicity assessment[a]	~20 mL/~10 mL	
Obtain nasal (midturbinate) swab (self-swab at home or by site staff at an in-person visit)	X	X
Collect AEs and SAEs as appropriate[b]	X	

a. Only if the participant has no blood sample collected in the previous 7 days. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
b. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no licensed vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

As more data about COVID-19 continue to accrue, the potential duration of protection afforded after a wild-type SARS-CoV-2 infection, and by vaccination, remains unknown. In addition, mutated SARS-CoV-2 VOCs have started to emerge, for example in the UK (known as 20I/501Y.V1, VOC 202012/01, or B.1.1.7), SA (known as 20H/501Y.V2 or B.1.351), and Brazil (known as P.1).[4]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[5,6]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may

be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Two SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein-receptor binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding P2 S.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

In light of the unknowns regarding duration of protection, as well as the emerging VOCs, it is important to understand the boostability of BNT162, and potential heterologous protection against emerging VOC(s). A first step to address this will be to study an additional dose of BNT162b2 at 30 µg given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity.

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[7] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[8] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with the currently available therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.

- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.

- All participants 12 to 15 years of age will be included in the reactogenicity subset (see Section 8.2.2).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[9]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of an efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	• GMC/GMT and GMFR at the time of Dose 3 and 7 days and 1 month after Dose 3.	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels
	• GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers
	• GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives	Estimands	Endpoints
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Objectives[a]	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19 prior to 1 month after receipt of the second dose	In participants complying with the key protocol criteria (evaluable participants) 1 month after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 prior to 1 month after receipt of the second dose
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 through the blinded follow-up period in participants without evidence of infection or confirmed COVID-19 during the study	In participants complying with the key protocol criteria (evaluable participants) 6 months after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization	In participants who received BNT162b2 at initial randomization 6, 12, and 24 months after receipt of the second dose of study intervention: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for description of the manufacturing process.

Up until the final efficacy analysis, this protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than at the approximate time participants in Phase 2/3 reach Visit 4.

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162.

Participants are expected to participate for up to a maximum of approximately 26 months.

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 μg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 280 participants from each of the 2 age groups (12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those

This document can only be used to support any marketing authorisation application and any extentions or variations thereof
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Participants ≥16 years of age who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 2/3 placebo recipient ≥16 years of age who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4).

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.4. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.1.3, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation applications and any extensions or variations thereof
ema.europa.eu

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization. Note that participants <18 years of age cannot be enrolled in the EU.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

    Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Informed Consent:

5. Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - Chronic liver disease
    - Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
    - Resident in a long-term facility

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- BMI >30 kg/m^2
- Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;
    - Sore throat;
    - Diarrhea;
    - Vomiting.
2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.
3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.
4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 2 investigational RNA vaccine candidates, with the addition of saline placebo, are the 3 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	10-, 20-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. Participants ≥16 years of age who originally received placebo and accept the offer to receive BNT162b2 at defined points as part of the study will receive 1 dose of BNT162b2 at each additional vaccination visit (Visits 101 and 102) in accordance with the study's additional SoA (Section 1.3.3). The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162 at Visit 8a.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.umpar.el

sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

9. Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

To allow administration of BNT162b2 to participants who originally received placebo, site staff will be unblinded to individual participants' original study intervention allocation as the participants become eligible for vaccination under local/national recommendations or from 6 months after the second dose.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).
- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.
- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

- After the formal data release of the final efficacy analysis of at least 164 cases, which is considered the primary completion of the study efficacy objectives, additional statisticians and programmers will become unblinded at the participant level to prepare unblinded analyses and other regulatory activities. A group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study.

- After the study data used for submission become public, the blinded study team will also have access to those data, and become unblinded at a group level.

- When a participant who originally received placebo receives BNT162b2 per the SoA in Section 1.3.3, the study team will become unblinded to the participant's original study intervention allocation.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

Instructions on how to unblind participants ahead of administration of BNT162b2 to placebo recipients will be provided separately: this unblinding will NOT be performed in the IRT.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants). In addition, for Phase 1 participants who go on to receive a third dose of BNT162, concomitant vaccinations will be collected from the time the participant provides informed consent (for receipt of Vaccination 3) through and including Visit 8c (1 month after the third dose).

- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 and from 28 days prior to Visit 8a to Vist 8c for Phase 1 participants, and from 28 days prior to enrollment to Visit 3 for Phase 2/3 participants).

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, for whatever reason, a participant receives only 1 dose of BNT162b2, the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. For example, because of a medication error a participant receives only 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa); the participant can return at a later date for the unscheduled visit. In this situation:

- Obtain informed consent.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s).

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

available information should be used to determine vital status only as appropriately directed in accordance with local law.

If a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, they may request to know which study intervention they received for Vaccination(s) 1/2 without needing to reconsent.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately up to: 500 mL for participants in Phase 1, 110 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum. Additionally, 20 mL of blood for participants ≥16 years of age and 10 mL for participants in the 12- to 15-year age stratum will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 670 mL during the 24-month study period. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[10] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
  - Fever;
  - New or increased cough;
  - New or increased shortness of breath;
  - Chills;
  - New or increased muscle pain;
  - New loss of taste or smell;
  - Sore throat;
  - Diarrhea;
  - Vomiting.

  The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):
  - Fatigue;
  - Headache;
  - Nasal congestion or runny nose;
  - Nausea.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction*;
  - Admission to an ICU;
  - Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay
- Full-length S-binding or S1-binding IgG level assay
- RBD-binding IgG level assay (Phase 1 only)
- N-binding antibody assay

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

8.1.2. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.4.

The nasal swabs will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2. For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with Section 8.3.2.

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

8.2.2. Electronic Diary

Certain participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. In addition, participants 16 through 17 years of age enrolled under protocol amendment 9 and onwards will be included in the reactogenicity subset. All other participants, including those who originally received placebo and then received BNT162b2 under protocol amendment 10 and onwards, will not complete a reactogenicity e-diary but will have their local reactions and systemic events detected and reported as AEs in accordance with Section 8.3.2. Phase 1 participants who receive a third dose of BNT162b2 will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage in the reactogenicity e-diary for 7 days following administration of the study intervention.

The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[9]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the administration of the second dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeurope.ru

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Additionally, for those participants who originally received placebo but go on to receive BNT162b2 at Vaccinations 3 and 4, AEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) through and including Visit 103. SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) to approximately 6 months after the second dose of BNT162b2 (Visit 104).

For Phase 1 participants who go on to receive a third dose of BNT162, AEs and SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccination 3) through and including Visit 8c (1 month after the third dose).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Report Form.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

8.3.6. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.6.1. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

8.3.7. Cardiovascular and Death Events

Not applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.9. Adverse Events of Special Interest

Not applicable.

8.3.9.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.10. Medical Device Deficiencies

Not applicable.

8.3.11. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

Unless stated otherwise, all study visits are intended to be conducted in person at the study site. If this is not possible, because of local circumstances related to the COVID-19 pandemic, study procedures that do not require in-person participant contact may be performed by telehealth. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Irrespective of the nature of the contact, all visit procedures are expected to be performed on the same day.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Between Visits 8 and 9

All participants who have not already been unblinded, no later than at the approximate time participants in Phase 2/3 reach Visit 4, will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, he or she will move to the procedures in Section 8.16.

8.11.1.11. Visit 8a – Vaccination 3: (175 to 315 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of a third dose of BNT162, his or her next visit should be Visit 9.

- Confirm that the participant originally received 10-µg, 20-µg, or 30-µg doses of BNT162b1 or BNT162b2 at Vaccinations 1 and 2. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Record nonstudy vaccinations as described in Section 6.5.
- Measure the participant's body temperature.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Ensure and document that inclusion criteria 2, 3, and 5 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met prior to vaccination.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer a 30-µg dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
    - Remind the participant of the e-diary technologies available for this study (see Section 8.14). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
    - Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.12):
        - Fever ≥39.0°C (≥102.1°F)
        - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units)
        - Severe pain at the injection site
        - Any severe systemic event

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
cms.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.12. Visit 8b – 1-Week Follow-up Visit (After Vaccination 3): (6 to 8 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

8.11.1.13. Visit 8c – 1-Month Follow-up Visit (After Vaccination 3): (28 to 35 Days After Visit 8a)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.14. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.15. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.

    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

    - Fever ≥39.0°C (≥102.1°F).

    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

    - Severe pain at the injection site.

    - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.

- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).

- Discuss contraceptive use as described in Section 10.4.

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- The investigator or an authorized designee completes the CRFs.
- If Visit 3 is being conducted under amendment 12 onward: If the participant is ≥16 years of age, and is eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, determine if he/she is willing to receive BNT162b2 as part of the study. If so, unblind the participant's study intervention assignment, and move placebo recipients to the procedures in Section 8.16.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- If not already unblinded, unblind the participant's study intervention assignment, and move placebo recipients willing to receive BNT162b2 to the procedures in Section 8.16.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

This document cannot be used to support and marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;

- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;

- Fever;

- New or increased cough;

- New or increased shortness of breath;

- Chills;

- New or increased muscle pain;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
  - Symptoms and signs, including
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
    - Significant acute renal, hepatic, or neurologic dysfunction

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

  - Clinical diagnosis

  - Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.

  - Full blood count

  - Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein

  - Imaging results (eg, CT or MRI scan) to document neurologic dysfunction

  - Number and type of any healthcare contact; duration of hospitalization and ICU stay

  - Death

- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

8.15. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 or 14 days after receipt of the second dose, depending on the objective) of past SARS-CoV-2 infection.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

- Asymptomatic SARS-CoV-2 infection surveillance visits: To determine the incidence of asymptomatic SARS-CoV-2 infection.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, asymptomatic SARS-CoV-2 infection surveillance visit swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result, either asymptomatic or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result), prior to Visit 2 should receive Vaccination 2 as normal.

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

If a participant ≥16 years of age becomes eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study.

Placebo recipients ≥16 years of age who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Dose 2, and will follow the procedures listed in this section for the remainder of their participation in the study. For Phase 2/3 participants, Visit 101 could occur at the same time as the original Visit 4.

8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant originally received only placebo at Vaccination 1/2. Secondary confirmation by another site staff member is required.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Review and consider inclusion criteria 2, 3, and 5 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 4 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101)

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Record AEs as described in Section 8.3.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Review and consider inclusion criteria 2, 3, and 5 and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record AEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 103 (if any).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment to call the participant by telephone for the next study contact.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 104 (if any).

- Request the return of the participant's e-diary or assist the participant/participant's parent(s)/legal guardian to remove the study application from his or her own personal device.

- Inform the participant/participant's parent(s)/legal guardian that his or her study participation has ended.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.17. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11 until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The surveillance will be conducted per the procedures listed below.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection.

8.17.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11

Before surveillance begins and any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

The visit should be conducted only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1) and this visit should be temporarily delayed until the symptoms have resolved.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 3 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Record AEs as described in Section 8.3 (only if the participant remains in the AE reporting period; see Section 8.3.1).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Ask the participant to obtain a surveillance self-swab at home in approximately 14 days or schedule an appointment for the participant to return to collect the swab at the site. The swab should be collected only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1).

This document cannot be used to support any Marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection

This is a repeating swab collection and will be conducted approximately every 14 days until the intensive surveillance period ends.

- Participant collects a self-swab and ships it to the site for assessment at the central laboratory. The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).
- Complete the source documents with the swab information.
- The investigator or an authorized designee completes the CRFs with the swab information.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by all-available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either $VE_1 > 30\%$ or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated based on the lower bound of the 95% CI. VE will be demonstrated if the lower bound of the 2-sided 95% CI for VE is >20%.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2**.** If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

9.2. Sample Size Determination

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection will be assessed in Phase 2/3 participants (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT). Assuming a true VE of 70%, a total of 53 asymptomatic cases will provide approximately 90% power to conclude true VE >20%. A total of 206 cases is needed to have 90% power if the true VE is 50%. The hypothesis for asymptomatic seroconversion of N-binding antibody will be tested if at least 206 cases are accrued. The hypothesis for asymptomatic infection based on central laboratory–confirmed NAAT in participants who are consented to participate in the intensive surveillance phase will be tested if at least 53 cases are accrued.

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 280 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants (or 280 vaccine recipients) per age group

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

will provide a power of 90.4% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.65	-0.2	225	90.4%

Abbreviation: GMR = geometric mean ratio.
a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).
b. At 0.05 alpha level (2-sided).

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	Dose 1 all-available: All randomized participants who receive at least 1 vaccination. Dose 2 all-available: All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention. Analyses of reactogenicity endpoints will be based on a subset of the safety population that includes participants with any e-diary data reported after vaccination.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Endpoint	Statistical Analysis Methods
Secondary immunogenicity (Phase 1)	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Endpoint	Statistical Analysis Methods
	For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Endpoint	Statistical Analysis Methods
	the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the 16- to 25-year age group)	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and 2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment. The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Endpoint	Statistical Analysis Methods
Exploratory immunogenicity (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2: **GMTs/GMCs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level** GMTs/GMCs and 2-sided 95% CIs will be provided by initial vaccine and age group for the following time points: • At Dose 3 and 7 days and 1 month after Dose 3 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 reference-strain neutralizing titers, SARS-CoV-2 SA-variant neutralizing titers, and full-length S-binding or S1-binding IgG level** GMFRs from Dose 3 to 7 days and 1 month after Dose 3 and 2-sided 95% CIs will be provided by initial vaccine and age group. GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **GMRs of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2** GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed reference-strain titers for each participant (1 month after Dose 3 – 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by

This document cannot be used to support any marketing authorisation application and and extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Endpoint	Statistical Analysis Methods
	constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. **GMRs of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2** GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (SA-variant titer at 1 month after Dose 3 – reference-strain titer at 1 month after Dose 2) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.
Exploratory immunogenicity (Phase 2/3)	**GMTs/GMCs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3:

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	• 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels after Dose 1 and after Dose 2.

9.4.2. Efficacy Analyses

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.
Secondary	**First: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Second: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Endpoint	Statistical Analysis Methods
	Third and fourth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group **Fifth and sixth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints for COVID-19 illness according to CDC-defined symptoms will be evaluated descriptively with 95% CIs. **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days or from 14 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[10] Missing efficacy data will not be imputed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Endpoint	Statistical Analysis Methods
	The following secondary efficacy endpoints regarding asymptomatic SARS-CoV-2 infection will be evaluated based on a success criterion of the lower bound of the 2-sided 95% CI for VE being >20%. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 prior to 1 month after receipt of the second dose for the active vaccine group to the placebo group** An asymptomatic case is defined as a positive N-binding antibody result at a post–Dose 2 visit (eg, Visit 3, 1 month after Dose 2) in participants without serological or virological evidence of infection prior to that visit, determined by a negative N-binding antibody result at Visit 1 and negative NAAT results at Visit 1 and Visit 2 and at the time of a potential COVID-19 illness. A secondary definition will be applied without the requirement for a negative NAAT result at Visit 2. VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection per 1000 person-years of follow-up in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants without evidence of infection (up to the start of asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The analysis will be based on the evaluable efficacy population and the all-available efficacy population and will include only participants who are consented to participate in the asymptomatic surveillance and who do not have serological or virological evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Endpoint	Statistical Analysis Methods
Exploratory	**Ratios of confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants without, and with and without, evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** After the primary objectives are met at the final analysis of at least 164 first primary cases, the study will continue with blinded follow-up until the participant is unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. Descriptive update of VE will be provided with additional follow-up data. VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[10] Supportive analysis of time to confirmed COVID-19 illness will be performed using Kaplan-Meier cumulative incidence curves. Participants who were randomized to placebo will be censored at the time of receipt of BNT162b2. **Incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness from 7 days after the second dose will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted. **Ratio of asymptomatic SARS-CoV-2 infection through the blinded follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection in the active vaccine group to the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Endpoint	Statistical Analysis Methods
	corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. **Incidence of asymptomatic SARS-CoV-2 infection through the entire study follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants who received BNT162b2 and who have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for asymptomatic infection will be provided for participants who received BNT162b2 at initial randomization and have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with evidence of infection (up to the start of the asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. Participants who are consented to participate in the asymptomatic surveillance and who have serological or virologic evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period will be included in the analysis.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Endpoint	Statistical Analysis Methods
	For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[11] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group. AEs and SAEs reported during the open-label follow-up period will be summarized separately for participants who were unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Endpoint	Statistical Analysis Methods
	The safety analyses are based on the safety population. Analyses of reactogenicity endpoints are based on a subset of the safety population that includes participants with any e-diary data reported after vaccination. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory (Phase 1)	For Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2: Descriptive statistics will be provided by initial vaccine and age group for local reactions and systemic events from Day 1 through Day 7 after Dose 3, and AEs/SAEs from Dose 3 to 1 month after Dose 3. Local reactions and systemic events from Day 1 through Day 7 after Dose 3 will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs.

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing “Process 1” and each lot of “Process 2” will be summarized descriptively. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing “Process 1” will be selected randomly for the analysis.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1-VE)/(2-VE)$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 6 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8, for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall Type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

Only the first primary endpoint will be analyzed at IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints (confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and in all participants, confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection and in all participants) will be evaluated sequentially in the stated order, by the same method used for the evaluation of primary VE endpoints. Success thresholds for secondary VE endpoints will be appropriately chosen to control overall Type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Complete safety and immunogenicity analysis approximately 1 month after Dose 3 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

(with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.

- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.
- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.
- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2.
- Analysis of efficacy against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) when a sufficient number of cases have accrued to evaluate the objective(s).
- Complete safety and efficacy analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.
- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met
- Review of safety and/or immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Up until the final efficacy analysis, 3 blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial. When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Abbreviation	Term
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
non-S	nonspike protein
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SA	South Africa
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Abbreviation	Term
UK	United Kingdom
ULN	upper limit of normal
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
VOC	variant of concern
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs after accrual of at least 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.

4 Centers for Disease Control and Prevention. Emerging SARS-CoV-2 variants. Available from: https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html. Updated: 28 Jan 2021. Accessed: 10 Feb 2021.

5 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

6 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

7 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

8 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

9 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

10 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

11 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 13, Clean Copy, 12Feb2021
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	12-Feb-2021 17:28:16	Business Line Approver
PPD	12-Feb-2021 18:13:38	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19645c712\Approved\Approved On: 12-Feb-2021 18:13 (GMT)

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 12	14 January 2021	• Because of a formatting error in protocol amendment 11, exclusion criterion 4 was inadvertently added to exclusion criterion 3 and the subsequent criteria renumbered. This amendment corrects that error. • Because of a change in the pace with which participants ≥16 years of age who originally received placebo will become eligible for receipt of BNT162b2, text was updated throughout the protocol to reflect that this will happen in a phased manner, with recommendations detailed separately and available in the electronic study reference portal. • Clarified that participants who are unblinded because they become potentially eligible for receipt of BNT162b2 will not participate in surveillance for asymptomatic SARS CoV-2 infection. • Corrected the exploratory objective to describe non-S seroconversion to SARS-CoV-2 to clarify that this will only include participants who received BNT162b2 at initial randomization (since those who received it subsequently do not have blood drawn). • In line with current recommendations, removed the requirement to discontinue study intervention because of a diagnosis of COVID-19 during the study.

Protocol amendment 11	04 January 2021	• Added approaches to evaluate efficacy against asymptomatic SARS-CoV-2 infection:
		  • Added objectives, estimands, and endpoints, and statistical methods, for assessment via N-binding antibody seroconversion;
		  • Added a potential intensive surveillance period for nasal swabbing, for assessment via NAAT:
		  • Corresponding objectives, estimands, and endpoints added
		  • Corresponding SoA and procedures added
		  • Details added in the statistical methods sections.
		• Added the possibility of assessing full-length S-binding, instead of S1-binding, IgG levels in Phase 2/3.
		• Clarified in Section 4.1.1 that any Phase 1 placebo recipient who has not already been

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		offered the opportunity to receive BNT162b2 will be given this opportunity at the approximate time participants in Phase 2/3 reach Visit 4, for consistency with other sections. • Added a sentence to reflect that assent is obtained from participants <18 years of age.
Protocol amendment 10	01 December 2020	• Added the possibility of administering BNT162b2 to participants who originally received placebo, following any local or national recommendations. • Added the possibility of administering BNT162b2 to participants who originally received placebo, following completion of the active safety surveillance period. • Added corresponding exploratory objectives and statistical analysis details. • Removed immunogenicity analyses of titers greater than defined threshold(s). • Removed the need for blinded COVID-19 case review after the final efficacy analysis. • Included the possibility, due to local circumstances related to the COVID-19 pandemic, that study procedures that do not require in-person participant contact may be performed by telehealth. • In light of additional information to better estimate the standard deviation of SARS-CoV-2 neutralizing titers, increased the sample size for the noninferiority immunogenicity analysis in adolescents 12 to 15 years of age.
Protocol amendment 9	29 October 2020	• To better align with the natural history of SARS-CoV-2 infection, added Phase 2/3 secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days after the second dose; also modified the existing secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days, as well as 7 days, after the second dose; • Made corresponding changes to the study design, study assessments and procedures, and statistical analysis sections. • For operational reasons, removed the interim analysis planned after accrual of 32 cases. • Clarified that interim analyses will be conducted after accrual of *at least* 62, 92, and 120 cases. • Included any participants 16 through 17 years of age enrolled under this amendment in the reactogenicity subset.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Added an unblinded clinical scientist to support DMC activities. • Clarified that serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.
Protocol amendment 8	15 October 2020	• Removed "N-binding antibody" and "SARS-CoV-2 detection by NAAT" as endpoints from the third exploratory objective, as these results are used for the determination of the population, and are not endpoints. • Clarified that the "Process 1" participants included in the descriptive analysis of "Process 1"- and "Process 2"-manufactured study interventions will be selected randomly. • Clarified that surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study. • Further modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Clarified that for participants who are not in the reactogenicity subset, local reactions and systemic events following vaccination should be detected and reported as AEs. • Clarified that premenarchal females are not WOCBP. • Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2. • Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2." • Clarified the degree of unblinding on the unblinded submissions team in Section 6.3.3. • Made provision for a second dose of BNT162b2 in participants who were affected by a medication error at Visit 2 in Section 6.6.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Provided further clarification regarding discontinuation of study intervention in Section 7.1. • Modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Added that 2 periods of potential COVID-19 symptoms within 4 days will be considered as a single illness. • Provided guidance in Section 8.13 regarding circumstances in which a SARS-CoV-2 test might be required even if symptoms within 7 days following each vaccination are considered more likely due to vaccine reactogenicity. • Made allowance in Section 8.13 for a second SARS-CoV-2 test to be performed within the same potential COVID-19 illness if it is in accordance with routine practice. • Added Section 8.15 to describe the reporting of SARS-CoV-2 test results and their implications for participants receiving a second vaccine dose. • Added statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age. • Amended scope of analyses of safety data in Section 9.5.1. • Made various editorial changes.
Protocol amendment 6 (Germany-specific)	23 September 2020	• According to regulatory request, inclusion criterion 1 now specifies that participants less than 18 years of age will not be enrolled in the EU.
Protocol amendment 6	08 September 2020	• Reordered some procedures in the Phase 2/3 schedule of activities for consistency with the main body of the protocol. • Corrected the window for the 6-month follow-up visit to be approximately 6 months after Vaccination 2. • Reduced the volume of blood draws to ~20 mL. • Removed the need to have safety data reported for participants to be included in the safety objective assessment. • Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease. • Increased the sample size for Phase 2/3 to ~43,998.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified that inclusion criterion 4 (ie, participants at higher risk for acquiring COVID-19) is applicable for Phase 2/3 only, and provided some examples. • Removed exclusion criterion 2 (ie, known infection with HIV, HCV, or HBV) for Phase 3 and added criteria for HIV-positive participants. • Decreased the lower age limit and removed the upper age limit for inclusion in Phase 2/3 in order to evaluate BNT162b2 30 µg in older adolescents and those over 85 years of age; updated the title and other references to adults to align with this change. • Renamed the immunological assays to align with other program-level documents. • Removed reference to the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) being "heads up." • Clarified that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention. • Added clarification that potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. • Updated the analysis population descriptions to align with the study SAP.
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory. • Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7. • Updated the stopping and alert rule parameters for enhanced COVID-19.
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation, and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol. • To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01):

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial • Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

TABLE OF CONTENTS

LIST OF TABLES 18
1. PROTOCOL SUMMARY 20
1.1. Synopsis 20
1.2. Schema 29
1.3. Schedule of Activities 30
1.3.1. Phase 1 30
1.3.2. Phase 2/3 36
1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo 40
1.3.4. Surveillance for Asymptomatic SARS-CoV-2 Infection 42
2. INTRODUCTION 43
2.1. Study Rationale 43
2.2. Background 43
2.2.1. Clinical Overview 44
2.3. Benefit/Risk Assessment 44
2.3.1. Risk Assessment 46
2.3.2. Benefit Assessment 48
2.3.3. Overall Benefit/Risk Conclusion 48
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 48
3.1. For Phase 1 48
3.2. For Phase 2/3 50
4. STUDY DESIGN 54
4.1. Overall Design 54
4.1.1. Phase 1 54
4.1.2. Phase 2/3 56
4.2. Scientific Rationale for Study Design 58
4.3. Justification for Dose 58
4.4. End of Study Definition 59
5. STUDY POPULATION 59
5.1. Inclusion Criteria 59
5.2. Exclusion Criteria 60

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

5.3. Lifestyle Considerations 63
5.3.1. Contraception 63
5.4. Screen Failures 63
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 63
6. STUDY INTERVENTION 64
6.1. Study Intervention(s) Administered 65
6.1.1. Manufacturing Process 65
6.1.2. Administration 65
6.2. Preparation/Handling/Storage/Accountability 66
6.2.1. Preparation and Dispensing 67
6.3. Measures to Minimize Bias: Randomization and Blinding 67
6.3.1. Allocation to Study Intervention 67
6.3.2. Blinding of Site Personnel 68
6.3.3. Blinding of the Sponsor 68
6.3.4. Breaking the Blind 69
6.4. Study Intervention Compliance 69
6.5. Concomitant Therapy 70
6.5.1. Prohibited During the Study 70
6.5.2. Permitted During the Study 71
6.6. Dose Modification 71
6.7. Intervention After the End of the Study 72
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 72
7.1. Discontinuation of Study Intervention 72
7.2. Participant Discontinuation/Withdrawal From the Study 72
7.2.1. Withdrawal of Consent 73
7.3. Lost to Follow-up 73
8. STUDY ASSESSMENTS AND PROCEDURES 74
8.1. Efficacy and/or Immunogenicity Assessments 75
8.1.1. Biological Samples 77
8.1.2. Surveillance for Asymptomatic SARS-CoV-2 Infection 78

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

8.2. Safety Assessments 78
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 79
8.2.2. Electronic Diary 79
8.2.2.1. Grading Scales 80
8.2.2.2. Local Reactions 80
8.2.2.3. Systemic Events 81
8.2.2.4. Fever 82
8.2.2.5. Antipyretic Medication 83
8.2.3. Phase 1 Stopping Rules 83
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 84
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 85
8.2.6. Pregnancy Testing 85
8.3. Adverse Events and Serious Adverse Events 85
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 85
8.3.1.1. Reporting SAEs to Pfizer Safety 86
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 87
8.3.2. Method of Detecting AEs and SAEs 87
8.3.3. Follow-up of AEs and SAEs 87
8.3.4. Regulatory Reporting Requirements for SAEs 87
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 88
8.3.5.1. Exposure During Pregnancy 88
8.3.5.2. Exposure During Breastfeeding 90
8.3.5.3. Occupational Exposure 90
8.3.6. Cardiovascular and Death Events 90
8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 91
8.3.8. Adverse Events of Special Interest 91
8.3.8.1. Lack of Efficacy 91
8.3.9. Medical Device Deficiencies 91
8.3.10. Medication Errors 91

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.4. Treatment of Overdose 92
8.5. Pharmacokinetics 93
8.6. Pharmacodynamics 93
8.7. Genetics 93
8.8. Biomarkers 93
8.9. Immunogenicity Assessments 93
8.10. Health Economics 93
8.11. Study Procedures 93
8.11.1. Phase 1 94
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 94
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 95
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 97
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 98
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 99
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 101
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 103
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 104
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4) 104
8.11.1.10. Between Visits 8 and 9 105
8.11.1.11. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2 105
8.11.1.12. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2 106
8.11.2. Phase 2/3 106
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 106

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 109
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2) 111
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2) 112
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 112
8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 113
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 114
8.13. COVID-19 Surveillance (All Participants) 115
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 116
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit) 117
8.14. Communication and Use of Technology 118
8.15. SARS-CoV-2 NAAT Results 118
8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo 119
8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2) 119
8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101) 121
8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102) 122
8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102) 122
8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102) 123
8.17. Surveillance for Asymptomatic SARS-CoV-2 Infection 123
8.17.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11 123

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

8.17.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection 124
9. STATISTICAL CONSIDERATIONS 125
9.1. Estimands and Statistical Hypotheses 125
9.1.1. Estimands 125
9.1.2. Statistical Hypotheses 126
9.1.2.1. Statistical Hypothesis Evaluation for Efficacy 126
9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity 126
9.2. Sample Size Determination 127
9.3. Analysis Sets 129
9.4. Statistical Analyses 129
9.4.1. Immunogenicity Analyses 130
9.4.2. Efficacy Analyses 134
9.4.3. Safety Analyses 139
9.4.4. Other Analyses 140
9.5. Interim Analyses 141
9.5.1. Analysis Timing 143
9.6. Data Monitoring Committee or Other Independent Oversight Committee 144
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 145
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 145
10.1.1. Regulatory and Ethical Considerations 145
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 146
10.1.2. Informed Consent Process 146
10.1.3. Data Protection 147
10.1.4. Dissemination of Clinical Study Data 148
10.1.5. Data Quality Assurance 149
10.1.6. Source Documents 150
10.1.7. Study and Site Start and Closure 151
10.1.8. Sponsor's Qualified Medical Personnel 151
10.2. Appendix 2: Clinical Laboratory Tests 153

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 155
10.3.1. Definition of AE 155
10.3.2. Definition of SAE 156
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 158
10.3.4. Reporting of SAEs 161
10.4. Appendix 4: Contraceptive Guidance 162
10.4.1. Male Participant Reproductive Inclusion Criteria 162
10.4.2. Female Participant Reproductive Inclusion Criteria 162
10.4.3. Woman of Childbearing Potential 163
10.4.4. Contraception Methods 164
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 166
10.6. Appendix 6: Abbreviations 168
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 172
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection 175
11. REFERENCES 176

LIST OF TABLES

Table 1. Local Reaction Grading Scale 81
Table 2. Systemic Event Grading Scale 81
Table 3. Scale for Fever 82
Table 4. Power Analysis for Noninferiority Assessment 128
Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 128
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility 142
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses 142
Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall 143
Table 9. Laboratory Abnormality Grading Scale 153
Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 173

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing application and any extensions or variations thereof
ema.europa.eu

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 174

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and efficacy of these prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Objectives[a]	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in <u>all participants</u> randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: ○ Local reactions (pain at the injection site, redness, and swelling) ○ Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100× (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19 prior to 1 month after receipt of the second dose	In participants complying with the key protocol criteria (evaluable participants) 1 month after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 prior to 1 month after receipt of the second dose
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Objectives[a]	Estimands	Endpoints
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 through the blinded follow-up period in participants without evidence of infection or confirmed COVID-19 during the study	In participants complying with the key protocol criteria (evaluable participants) 6 months after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization	In participants who received BNT162b2 at initial randomization 6, 12, and 24 months after receipt of the second dose of study intervention: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Objectives[a]	Estimands	Endpoints
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for a description of the manufacturing process.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Participants ≥16 years of age who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

This document cannot be used to support any marketing authorisation application and any variations or variations thereof
ema.europa.eu

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated. VE will be demonstrated if the lower bound of the 95% CI for VE is >20%.

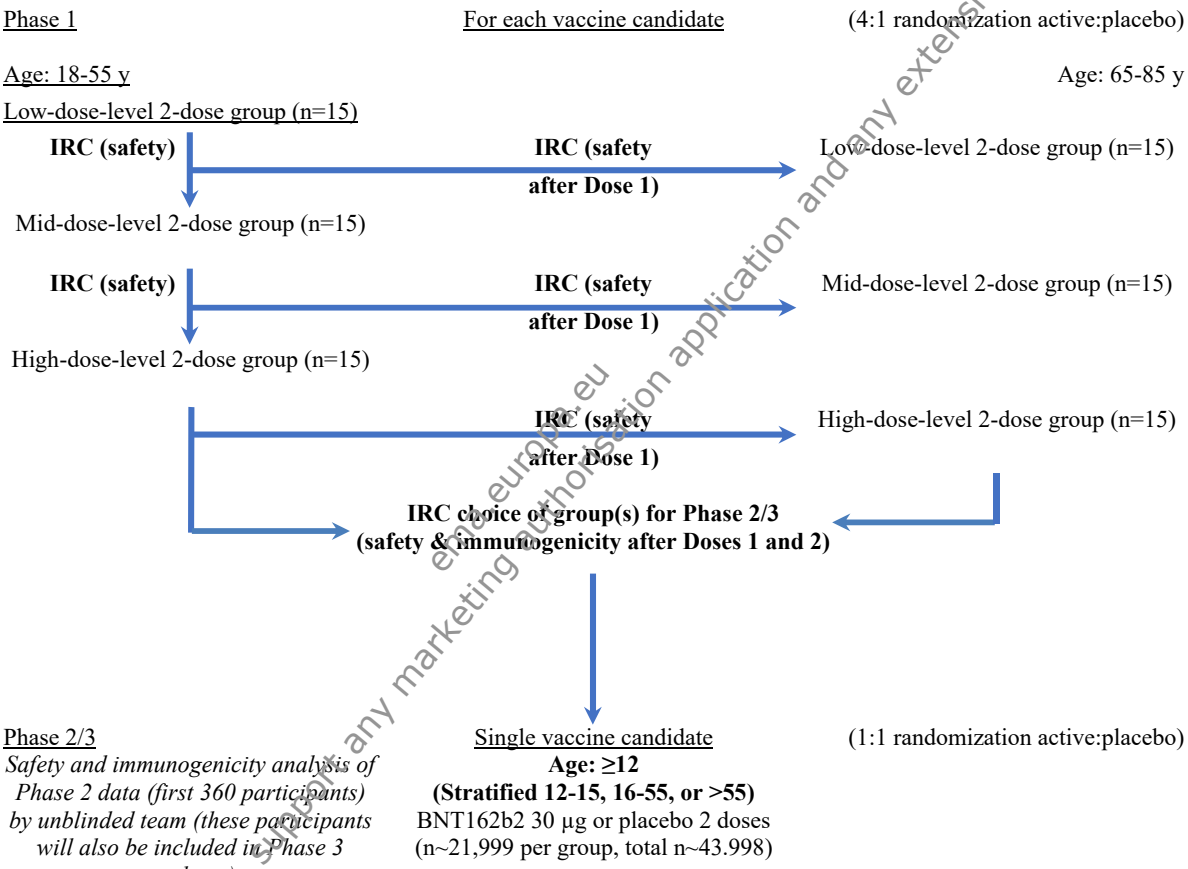
In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Except for the objective to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age, the other immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 neutralizing titers, full-length S-binding or S1-binding IgG levels, and/or RBD-binding IgG levels (Phase 1 only) at the various time points.

1.2. Schema



Abbreviation: IRC = internal review committee.

Note: Participants ⩾16 years of age who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b1 or BNT162b2 (at any dose level) will continue in the study as originally planned.

All other participants will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study no later than at the approximate time participants in Phase 2/3 reach Visit 4. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[c]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~20 mL	~20 mL	~20 mL		~20 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X								
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X											

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Provide thermometer and measuring device		X			X								
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		←	→	←	→								
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application											X		

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant ≥16 years of age becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 in a phased manner as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b2 or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b2 will continue in the study as originally planned.

All other participants ≥16 years of age who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4). If they want to receive BNT162b2, they will be unblinded and those who did originally receive placebo will move to the SoA in Section 1.3.3 for their remaining visits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X		
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL		~20 mL/ ~10 mL
Obtain nasal (midturbinate) swab	X	X					X	
Obtain randomization number and study intervention allocation	X							
Administer study intervention	X	X						

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	◄►	◄►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X	X[f]
According to eligibility, ascertain willingness to receive BNT162b2 if originally received placebo; if willing, unblind the participant's study intervention assignment (if not already done), and move placebo recipients to the SoA in Section 1.3.3			X ◄►	X				
Collect e-diary or assist the participant to delete application						X		

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants ≥16 years of age who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. Any placebo recipient ≥16 years of age who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2.

Visit Number	101	102	103	104	105	Unplanned	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm participant meets local/national recommending criteria or is at least 175 days after Vaccination 2 (Visit 4/Visit 2)	X						
Obtain informed consent	X						
Confirm participant originally received placebo	X						
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X					
Collect prohibited medication use	X	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X		
Confirm eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment	~20 mL						~20 mL
Obtain nasal (midturbinate) swab	X	X				X	
Obtain vaccine vial allocation via IRT	X	X					
Administer BNT162b2	X	X					

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	101	102	103	104	105	Unplanned	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Collect AEs and SAEs as appropriate	X	X	X	X		X[d]	X[d]
Contact the participant by telephone			X	X	X		
Request the participant return the e-diary or assist the participant to delete the application					X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)						X	X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

a. For participants who become eligible according to recommendations detailed separately and available in the electronic study reference portal.
b. For any remaining Phase 2/3 placebo recipients who wish to receive BNT162b2; may be combined with Visit 4 for Phase 2/3 participants.
c. Only if the participant has no blood sample collected in the previous 7 days.
d. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

1.3.4. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4 or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

Visit Number	201	202 Onward
Visit Description	**Asymptomatic SARS-CoV-2 Infection Surveillance Consent**	**Asymptomatic SARS-CoV-2 Infection Surveillance Swab**
Visit Window (Days)	**From Approval of Protocol Amendment 11**	**Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection**
Obtain informed consent for asymptomatic SARS-CoV-2 infection surveillance	X	
Collect prohibited medication use	X	
Collect blood sample for immunogenicity assessment[a]	~20 mL/~10 mL	
Obtain nasal (midturbinate) swab (self-swab at home or by site staff at an in-person visit)	X	X
Collect AEs and SAEs as appropriate[b]	X	

a. Only if the participant has no blood sample collected in the previous 7 days. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
b. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Two SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2-mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein-receptor binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding P2 S.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with the currently available

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.

- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.

- All participants 12 to 15 years of age will be included in the reactogenicity subset (see Section 8.2.2).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of an efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Objectives[a]	Estimands	Endpoints
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19 prior to 1 month after receipt of the second dose	In participants complying with the key protocol criteria (evaluable participants) 1 month after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 prior to 1 month after receipt of the second dose
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 through the blinded follow-up period in participants without evidence of infection or confirmed COVID-19 during the study	In participants complying with the key protocol criteria (evaluable participants) 6 months after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization	In participants who received BNT162b2 at initial randomization 6, 12, and 24 months after receipt of the second dose of study intervention: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for description of the manufacturing process.

Up until the final efficacy analysis, this protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
- Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination

- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than at the approximate time participants in Phase 2/3 reach Visit 4.

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 280 participants from each of the 2 age groups

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

(12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Participants ≥16 years of age who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 2/3 placebo recipient ≥16 years of age who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4).

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.4. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization. Note that participants <18 years of age cannot be enrolled in the EU.

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

Informed Consent:

5. Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

   - Hypertension

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Diabetes mellitus
- Chronic pulmonary disease
- Asthma
- Current vaping or smoking
- History of chronic smoking within the prior year
- Chronic liver disease
- Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
- Resident in a long-term facility
- BMI >30 kg/m^2
- Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Sore throat;
- Diarrhea;
- Vomiting.

2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.

3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 2 investigational RNA vaccine candidates, with the addition of saline placebo, are the 3 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	10-, 20-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. Participants ≥16 years of age who originally received placebo and accept the offer to receive BNT162b2 at defined points as part of the study will

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

receive 1 dose of BNT162b2 at each additional vaccination visit (Visits 101 and 102) in accordance with the study's additional SoA (Section 1.3.3). The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

9. Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

To allow administration of BNT162b2 to participants who originally received placebo, site staff will be unblinded to individual participants' original study intervention allocation as the participants become eligible for vaccination under local/national recommendations or from 6 months after the second dose.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).
- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.
- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

- After the formal data release of the final efficacy analysis of at least 164 cases, which is considered the primary completion of the study efficacy objectives, additional statisticians and programmers will become unblinded at the participant level to prepare unblinded analyses and other regulatory activities. A group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study.

- After the study data used for submission become public, the blinded study team will also have access to those data, and become unblinded at a group level.

- When a participant who originally received placebo receives BNT162b2 per the SoA in Section 1.3.3, the study team will become unblinded to the participant's original study intervention allocation.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

Instructions on how to unblind participants ahead of administration of BNT162b2 to placebo recipients will be provided separately: this unblinding will NOT be performed in the IRT.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).
- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.
- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants).

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, due to a medication error, a participant receives 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa), the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. In this situation:

- Obtain informed consent for administration of the additional dose.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s).

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately up to: 515 mL for participants in Phase 1, 110 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum. Additionally, 20 mL of blood for participants ≥16 years of age and 10 mL for participants in the 12- to 15-year age stratum will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 700 mL during the 24-month study period. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

period, either at the central laboratory or at a local testing facility (using an acceptable test):

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction*;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Admission to an ICU;
- Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay
- Full-length S-binding or S1-binding IgG level assay
- RBD-binding IgG level assay (Phase 1 only)
- N-binding antibody assay

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

development of other products, and/or for vaccine related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

8.1.2. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.4.

The nasal swabs will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2. For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with Section 8.3.2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Certain participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. In addition, participants 16 through 17 years of age enrolled under protocol amendment 9 and onwards will be included in the reactogenicity subset. All other participants, including those who originally received placebo and then received BNT162b2 under protocol amendment 10 and onwards, will not complete a reactogenicity e-diary but will have their local reactions and systemic events detected and reported as AEs in accordance with Section 8.3.2.

The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the last dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Additionally, for those participants who originally received placebo but go on to receive BNT162b2 at Vaccinations 3 and 4, AEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) through and including Visit 103. SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) to approximately 6 months after the second dose of BNT162b2 (Visit 104).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

Unless stated otherwise, all study visits are intended to be conducted in person at the study site. If this is not possible, because of local circumstances related to the COVID-19 pandemic, study procedures that do not require in-person participant contact may be performed by telehealth. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Irrespective of the nature of the contact, all visit procedures are expected to be performed on the same day.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.

- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Between Visits 8 and 9

All participants who have not already been unblinded, no later than at the approximate time participants in Phase 2/3 reach Visit 4, will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, he or she will move to the procedures in Section 8.16.

8.11.1.11. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

8.11.1.12. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.

- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
    - Severe pain at the injection site.
    - Any severe systemic event.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.

- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- If Visit 3 is being conducted under amendment 12 onward: If the participant is ≥16 years of age, and is eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, determine if he/she is willing to receive BNT162b2 as part of the study. If so, unblind the participant's study intervention assignment, and move placebo recipients to the procedures in Section 8.16.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- If not already unblinded, unblind the participant's study intervention assignment, and move placebo recipients willing to receive BNT162b2 to the procedures in Section 8.16.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;

- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;

- Fever;

- New or increased cough;

- New or increased shortness of breath;

- Chills;

- New or increased muscle pain;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
  - Symptoms and signs, including
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
    - Significant acute renal, hepatic, or neurologic dysfunction

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

  - Clinical diagnosis
  - Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.
  - Full blood count
  - Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
  - Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
  - Number and type of any healthcare contact; duration of hospitalization and ICU stay
  - Death
- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

8.15. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 or 14 days after receipt of the second dose, depending on the objective) of past SARS-CoV-2 infection.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

- Asymptomatic SARS-CoV-2 infection surveillance visits: To determine the incidence of asymptomatic SARS-CoV-2 infection.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, asymptomatic SARS-CoV-2 infection surveillance visit swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result, either asymptomatic or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result), prior to Visit 2 should receive Vaccination 2 as normal.

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

If a participant ≥16 years of age becomes eligible for receipt of BNT162b2 according to recommendations detailed separately and available in the electronic study reference portal, the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study.

Placebo recipients ≥16 years of age who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Dose 2, and will follow the procedures listed in this section for the remainder of their participation in the study. For Phase 2/3 participants, Visit 101 could occur at the same time as the original Visit 4.

8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant originally received only placebo at Vaccination 1/2. Secondary confirmation by another site staff member is required.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Ensure and document that inclusion criteria 2, 3, and 5 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 4 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101)

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Record AEs as described in Section 8.3.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that inclusion criteria 2, 3, and 5 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record AEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 103 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 104 (if any).
- Request the return of the participant's e-diary or assist the participant/participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Inform the participant/participant's parent(s)/legal guardian that his or her study participation has ended.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11 until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The surveillance will be conducted per the procedures listed below.

Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

8.17.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11

Before surveillance begins and any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

The visit should be conducted only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1) and this visit should be temporarily delayed until the symptoms have resolved.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 3 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Record AEs as described in Section 8.3 (only if the participant remains in the AE reporting period; see Section 8.3.1).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Ask the participant to obtain a surveillance self-swab at home in approximately 14 days or schedule an appointment for the participant to return to collect the swab at the site. The swab should be collected only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection

This is a repeating swab collection and will be conducted approximately every 14 days until the intensive surveillance period ends.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Participant collects a self-swab and ships it to the site for assessment at the central laboratory. The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- Complete the source documents with the swab information.

- The investigator or an authorized designee completes the CRFs with the swab information.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by all-available efficacy population. Missing laboratory

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either VE_1 >30% or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated based on the lower bound of the 95% CI. VE will be demonstrated if the lower bound of the 2-sided 95% CI for VE is >20%.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln(0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2**.** If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

9.2. Sample Size Determination

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection will be assessed in Phase 2/3 participants (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT). Assuming a true VE of 70%, a total of 53 asymptomatic cases will provide approximately 90% power to conclude true VE >20%. A total of 206 cases is needed to have 90% power if the true VE is 50%. The hypothesis for asymptomatic seroconversion of N-binding antibody will be tested if at least 206 cases are accrued. The hypothesis for asymptomatic infection based on central laboratory–confirmed NAAT in participants who are consented to participate in the intensive surveillance phase will be tested if at least 53 cases are accrued.

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 280 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.65	-0.2	225	90.4%

Abbreviation: GMR = geometric mean ratio.
a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).
b. At 0.05 alpha level (2-sided).

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 vaccination. 2. All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Endpoint	Statistical Analysis Methods
	GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the 16- to 25-year age group)	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and 2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment. The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Endpoint	Statistical Analysis Methods
	• 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Endpoint	Statistical Analysis Methods
	RCDCs for immunogenicity results Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level after Dose 1 and after Dose 2.

9.4.2. Efficacy Analyses

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Endpoint	Statistical Analysis Methods
	The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.
Secondary	**First: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Second: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Third and fourth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Fifth and sixth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints for COVID-19 illness according to CDC-defined symptoms will be evaluated descriptively with 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Endpoint	Statistical Analysis Methods
	Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days or from 14 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[9] Missing efficacy data will not be imputed. The following secondary efficacy endpoints regarding asymptomatic SARS-CoV-2 infection will be evaluated based on a success criterion of the lower bound of the 2-sided 95% CI for VE being >20%. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 prior to 1 month after receipt of the second dose for the active vaccine group to the placebo group** An asymptomatic case is defined as positive N-binding antibody at a post–Dose 2 visit (eg, Visit 3, 1 month after Dose 2) in participants without serological or virological evidence of infection prior to that visit, determined by negative N-binding antibody at Visit 1 and negative NAAT at Visit 1 and Visit 2 and at the time of a potential COVID-19 illness. A secondary definition will be applied without the requirement for a negative NAAT at Visit 2. VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection per 1000 person-years of follow-up in the active vaccine group to the corresponding infection in the placebo

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Endpoint	Statistical Analysis Methods
	group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants without evidence of infection (up to the start of asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The analysis will be based on the evaluable efficacy population and the all-available efficacy population and will include only participants who are consented to participate in the asymptomatic surveillance and who do not have serological or virological evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period.
Exploratory	**Ratios of confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants without, and with and without, evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** After the primary objectives are met at the final analysis of at least 164 first primary cases, the study will continue with blinded follow-up until the participant is unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. Descriptive update of VE will be provided with additional follow-up data. VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[9] Supportive analysis of time to confirmed COVID-19 illness will be performed using Kaplan-Meier cumulative incidence curves.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc ema europa eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Endpoint	Statistical Analysis Methods
	Participants who were randomized to placebo will be censored at the time of receipt of BNT162b2. **Incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness from 7 days after the second dose will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted. **Ratio of asymptomatic SARS-CoV-2 infection through the blinded follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. **Incidence of asymptomatic SARS-CoV-2 infection through the entire study follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants who received BNT162b2 and who have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for asymptomatic infection will be provided for participants who received BNT162b2 at initial randomization and have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with evidence of infection (up to the start of the asymptomatic surveillance period) for the active vaccine group to the placebo group**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Endpoint	Statistical Analysis Methods
	VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. Participants who are consented to participate in the asymptomatic surveillance and who have serological or virologic evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period will be included in the analysis.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition,

This document cannot be used to support a marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Endpoint	Statistical Analysis Methods
	for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group. AEs and SAEs reported during the open-label follow-up period will be summarized separately for participants who were unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory	N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" and each lot of "Process 2" will be summarized descriptively. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected randomly for the analysis.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Table 6 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8, for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall Type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

Only the first primary endpoint will be analyzed at IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints (confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and in all participants, confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection and in all participants) will be evaluated sequentially in the stated order, by the same method used for the evaluation of primary VE endpoints. Success thresholds for secondary VE endpoints will be appropriately chosen to control overall Type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data (with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.

- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.

- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2.

- Analysis of efficacy against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) when a sufficient number of cases have accrued to evaluate the objective(s).

- Complete safety and efficacy analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.

- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort

- Review of safety data in the case of a stopping rule being met

- Review of safety and/or immunogenicity data to:

  - Allow groups of participants of 65 to 85 years of age to proceed

  - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review

- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Whether any groups may not be started
- Whether any groups may be terminated early
- Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses

- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Up until the final efficacy analysis, 3 blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;

- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial. When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof in the European Union

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Abbreviation	Term
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
non-S	nonspike protein
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Abbreviation	Term
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs after accrual of at least 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.

4 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

5 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

6 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

7 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

8 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

9 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

10 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 12 Clean Copy, 14 Jan 2021
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY Individuals

Signed By:	Date(GMT)	Signing Capacity
PPD	14-Jan-2021 17:47:54	Business Line Approver
PPD	14-Jan-2021 18:47:06	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1960306a8\Approved\Approved On: 14-Jan-2021 18:47 (GMT)

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**

Protocol amendment 11	04 January 2021	• Added approaches to evaluate efficacy against asymptomatic SARS-CoV-2 infection:
		  • Added objectives, estimands, and endpoints, and statistical methods, for assessment via N-binding antibody seroconversion;
		  • Added a potential intensive surveillance period for nasal swabbing, for assessment via NAAT:
		  • Corresponding objectives, estimands, and endpoints added
		  • Corresponding SoA and procedures added
		  • Details added in the statistical methods sections.
		• Added the possibility of assessing full-length S-binding, instead of S1-binding, IgG levels in Phase 2/3.
		• Clarified in Section 4.1.1 that any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity at the approximate time participants in Phase 2/3 reach Visit 4, for consistency with other sections.
		• Added a sentence to reflect that assent is obtained from participants <18 years of age.

Protocol amendment 10	01 December 2020	• Added the possibility of administering BNT162b2 to participants who originally received placebo, following any local or national recommendations. • Added the possibility of administering BNT162b2 to participants who originally received placebo, following completion of the active safety surveillance period. • Added corresponding exploratory objectives and statistical analysis details. • Removed immunogenicity analyses of titers greater than defined threshold(s). • Removed the need for blinded COVID-19 case review after the final efficacy analysis. • Included the possibility, due to local circumstances related to the COVID-19 pandemic, that study procedures that do not require in-person participant contact may be performed by telehealth. • In light of additional information to better estimate the standard deviation of SARS-CoV-2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		neutralizing titers, increased the sample size for the noninferiority immunogenicity analysis in adolescents 12 to 15 years of age.
Protocol amendment 9	29 October 2020	• To better align with the natural history of SARS-CoV-2 infection, added Phase 2/3 secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days after the second dose; also modified the existing secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days, as well as 7 days, after the second dose; • Made corresponding changes to the study design, study assessments and procedures, and statistical analysis sections. • For operational reasons, removed the interim analysis planned after accrual of 32 cases. • Clarified that interim analyses will be conducted after accrual of *at least* 62, 92, and 120 cases. • Included any participants 16 through 17 years of age enrolled under this amendment in the reactogenicity subset. • Added an unblinded clinical scientist to support DMC activities. • Clarified that serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.
Protocol amendment 8	15 October 2020	• Removed “N-binding antibody” and “SARS-CoV-2 detection by NAAT” as endpoints from the third exploratory objective, as these results are used for the determination of the population, and are not endpoints. • Clarified that the “Process 1” participants included in the descriptive analysis of “Process 1”- and “Process 2”-manufactured study interventions will be selected randomly. • Clarified that surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study. • Further modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Clarified that for participants who are not in the reactogenicity subset, local reactions and systemic events following vaccination should be detected and reported as AEs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified that premenarchal females are not WOCBP. • Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2. • Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2." • Clarified the degree of unblinding on the unblinded submissions team in Section 6.3.3. • Made provision for a second dose of BNT162b2 in participants who were affected by a medication error at Visit 2 in Section 6.6. • Provided further clarification regarding discontinuation of study intervention in Section 7.1. • Modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Added that 2 periods of potential COVID-19 symptoms within 4 days will be considered as a single illness. • Provided guidance in Section 8.13 regarding circumstances in which a SARS-CoV-2 test might be required even if symptoms within 7 days following each vaccination are considered more likely due to vaccine reactogenicity. • Made allowance in Section 8.13 for a second SARS-CoV-2 test to be performed within the same potential COVID-19 illness if it is in accordance with routine practice. • Added Section 8.15 to describe the reporting of SARS-CoV-2 test results and their implications for participants receiving a second vaccine dose. • Added statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Amended scope of analyses of safety data in Section 9.5.1. • Made various editorial changes.
Protocol amendment 6 (Germany-specific)	23 September 2020	• According to regulatory request, inclusion criterion 1 now specifies that participants less than 18 years of age will not be enrolled in the EU.
Protocol amendment 6	08 September 2020	• Reordered some procedures in the Phase 2/3 schedule of activities for consistency with the main body of the protocol. • Corrected the window for the 6-month follow-up visit to be approximately 6 months after Vaccination 2. • Reduced the volume of blood draws to ~20 mL. • Removed the need to have safety data reported for participants to be included in the safety objective assessment. • Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease. • Increased the sample size for Phase 2/3 to ~43,998. • Clarified that inclusion criterion 4 (ie, participants at higher risk for acquiring COVID-19) is applicable for Phase 2/3 only, and provided some examples. • Removed exclusion criterion 2 (ie, known infection with HIV, HCV, or HBV) for Phase 3 and added criteria for HIV-positive participants. • Decreased the lower age limit and removed the upper age limit for inclusion in Phase 2/3 in order to evaluate BNT162b2 30 µg in older adolescents and those over 85 years of age; updated the title and other references to adults to align with this change. • Renamed the immunological assays to align with other program-level documents. • Removed reference to the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) being “heads up.” • Clarified that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention. • Added clarification that potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. • Updated the analysis population descriptions to align with the study SAP.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory. • Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7. • Updated the stopping and alert rule parameters for enhanced COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 17
1. PROTOCOL SUMMARY 19
1.1. Synopsis 19
1.2. Schema 28
1.3. Schedule of Activities 29
1.3.1. Phase 1 29
1.3.2. Phase 2/3 35
1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo 39
1.3.4. Surveillance for Asymptomatic SARS-CoV-2 Infection 41
2. INTRODUCTION 42
2.1. Study Rationale 42
2.2. Background 42
2.2.1. Clinical Overview 43
2.3. Benefit/Risk Assessment 43
2.3.1. Risk Assessment 45
2.3.2. Benefit Assessment 47
2.3.3. Overall Benefit/Risk Conclusion 47
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 47
3.1. For Phase 1 47
3.2. For Phase 2/3 49
4. STUDY DESIGN 53
4.1. Overall Design 53
4.1.1. Phase 1 53
4.1.2. Phase 2/3 55
4.2. Scientific Rationale for Study Design 57
4.3. Justification for Dose 57
4.4. End of Study Definition 58
5. STUDY POPULATION 58
5.1. Inclusion Criteria 58
5.2. Exclusion Criteria 59

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

5.3. Lifestyle Considerations 62
5.3.1. Contraception 62
5.4. Screen Failures 62
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 62
6. STUDY INTERVENTION 63
6.1. Study Intervention(s) Administered 64
6.1.1. Manufacturing Process 64
6.1.2. Administration 64
6.2. Preparation/Handling/Storage/Accountability 65
6.2.1. Preparation and Dispensing 66
6.3. Measures to Minimize Bias: Randomization and Blinding 66
6.3.1. Allocation to Study Intervention 66
6.3.2. Blinding of Site Personnel 67
6.3.3. Blinding of the Sponsor 67
6.3.4. Breaking the Blind 68
6.4. Study Intervention Compliance 68
6.5. Concomitant Therapy 69
6.5.1. Prohibited During the Study 69
6.5.2. Permitted During the Study 70
6.6. Dose Modification 70
6.7. Intervention After the End of the Study 71
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 71
7.1. Discontinuation of Study Intervention 71
7.2. Participant Discontinuation/Withdrawal From the Study 71
7.2.1. Withdrawal of Consent 72
7.3. Lost to Follow-up 72
8. STUDY ASSESSMENTS AND PROCEDURES 73
8.1. Efficacy and/or Immunogenicity Assessments 74
8.1.1. Biological Samples 76
8.1.2. Surveillance for Asymptomatic SARS-CoV-2 Infection 77

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

8.2. Safety Assessments 77
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 78
8.2.2. Electronic Diary 78
8.2.2.1. Grading Scales 79
8.2.2.2. Local Reactions 79
8.2.2.3. Systemic Events 80
8.2.2.4. Fever 81
8.2.2.5. Antipyretic Medication 82
8.2.3. Phase 1 Stopping Rules 82
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 83
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 84
8.2.6. Pregnancy Testing 84
8.3. Adverse Events and Serious Adverse Events 84
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 84
8.3.1.1. Reporting SAEs to Pfizer Safety 85
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 86
8.3.2. Method of Detecting AEs and SAEs 86
8.3.3. Follow-up of AEs and SAEs 86
8.3.4. Regulatory Reporting Requirements for SAEs 86
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 87
8.3.5.1. Exposure During Pregnancy 87
8.3.5.2. Exposure During Breastfeeding 89
8.3.5.3. Occupational Exposure 89
8.3.6. Cardiovascular and Death Events 89
8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 90
8.3.8. Adverse Events of Special Interest 90
8.3.8.1. Lack of Efficacy 90
8.3.9. Medical Device Deficiencies 90
8.3.10. Medication Errors 90

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.4. Treatment of Overdose 91
8.5. Pharmacokinetics 92
8.6. Pharmacodynamics 92
8.7. Genetics 92
8.8. Biomarkers 92
8.9. Immunogenicity Assessments 92
8.10. Health Economics 92
8.11. Study Procedures 92
8.11.1. Phase 1 93
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 93
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 94
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 96
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 97
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 98
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 100
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 102
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 103
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4) 103
8.11.1.10. Between Visits 8 and 9 104
8.11.1.11. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2 104
8.11.1.12. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2 105
8.11.2. Phase 2/3 105
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 105

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 108
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2) 110
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2) 111
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 111
8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 112
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 113
8.13. COVID-19 Surveillance (All Participants) 114
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 115
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit) 116
8.14. Communication and Use of Technology 117
8.15. SARS-CoV-2 NAAT Results 117
8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo 118
8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2) 118
8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101) 120
8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102) 121
8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102) 121
8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102) 122
8.17. Surveillance for Asymptomatic SARS-CoV-2 Infection 123
8.17.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11 123

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

8.17.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection 124
9. STATISTICAL CONSIDERATIONS 124
9.1. Estimands and Statistical Hypotheses 125
9.1.1. Estimands 125
9.1.2. Statistical Hypotheses 125
9.1.2.1. Statistical Hypothesis Evaluation for Efficacy 125
9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity 126
9.2. Sample Size Determination 126
9.3. Analysis Sets 128
9.4. Statistical Analyses 129
9.4.1. Immunogenicity Analyses 129
9.4.2. Efficacy Analyses 133
9.4.3. Safety Analyses 138
9.4.4. Other Analyses 140
9.5. Interim Analyses 140
9.5.1. Analysis Timing 143
9.6. Data Monitoring Committee or Other Independent Oversight Committee 144
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 145
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 145
10.1.1. Regulatory and Ethical Considerations 145
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 146
10.1.2. Informed Consent Process 146
10.1.3. Data Protection 147
10.1.4. Dissemination of Clinical Study Data 147
10.1.5. Data Quality Assurance 149
10.1.6. Source Documents 150
10.1.7. Study and Site Start and Closure 150
10.1.8. Sponsor's Qualified Medical Personnel 151
10.2. Appendix 2: Clinical Laboratory Tests 152

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 154
10.3.1. Definition of AE 154
10.3.2. Definition of SAE 155
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 157
10.3.4. Reporting of SAEs 160
10.4. Appendix 4: Contraceptive Guidance 161
10.4.1. Male Participant Reproductive Inclusion Criteria 161
10.4.2. Female Participant Reproductive Inclusion Criteria 161
10.4.3. Woman of Childbearing Potential 162
10.4.4. Contraception Methods 163
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 165
10.6. Appendix 6: Abbreviations 167
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 171
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection 174
11. REFERENCES 175

LIST OF TABLES

Table 1. Local Reaction Grading Scale 80
Table 2. Systemic Event Grading Scale 80
Table 3. Scale for Fever 81
Table 4. Power Analysis for Noninferiority Assessment 127
Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 128
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility 141
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses 142
Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall 142
Table 9. Laboratory Abnormality Grading Scale 152
Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 172

This document cannot be used to support any marketing application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 173

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and efficacy of these prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Objectives[a]	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: ○ Local reactions (pain at the injection site, redness, and swelling) ○ Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100× (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19 prior to 1 month after receipt of the second dose	In participants complying with the key protocol criteria (evaluable participants) 1 month after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 prior to 1 month after receipt of the second dose
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Objectives[a]	Estimands	Endpoints
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 through the blinded follow-up period in participants without evidence of infection or confirmed COVID-19 during the study	In participants complying with the key protocol criteria (evaluable participants) 6 months after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 at initial randomization 6, 12, and 24 months after receipt of the second dose of study intervention: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for a description of the manufacturing process.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document can only be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Participants ≥16 years of age who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated. VE will be demonstrated if the lower bound of the 95% CI for VE is >20%.

In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

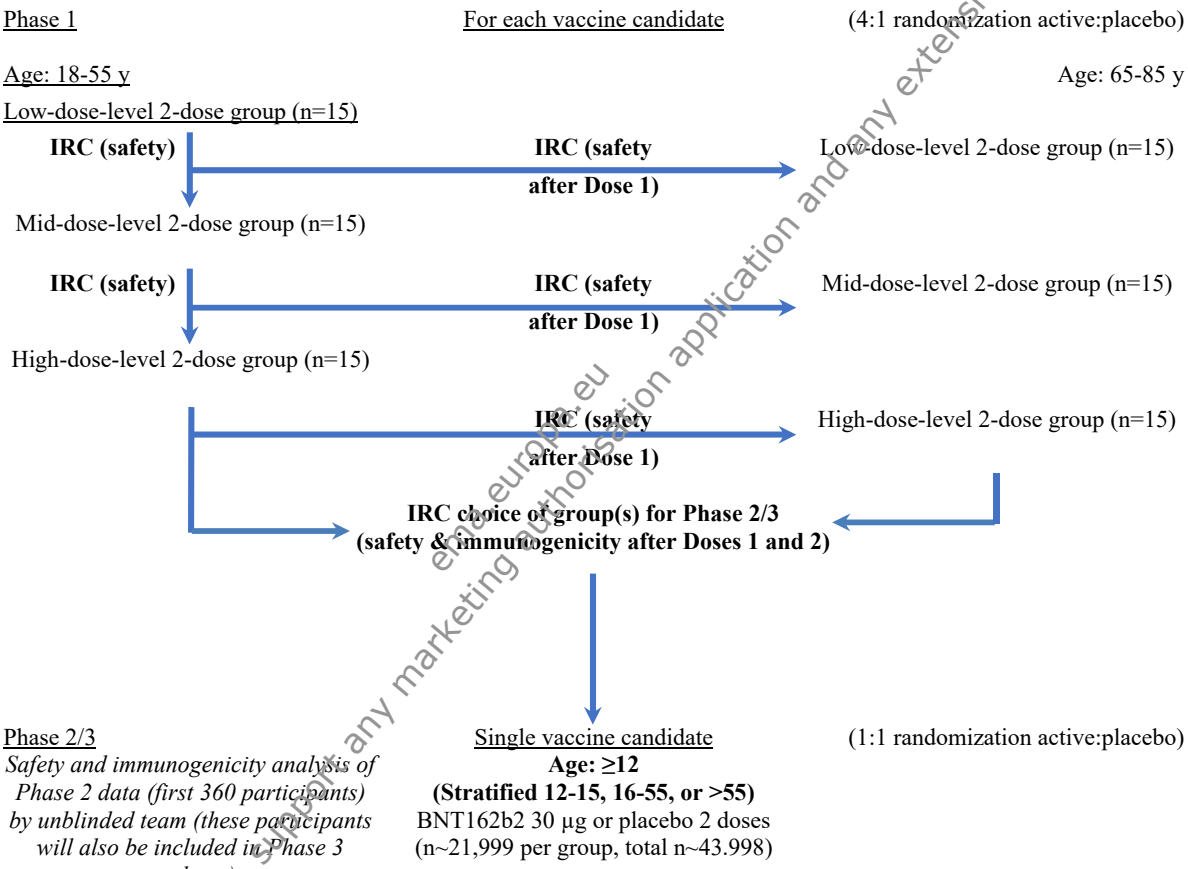
The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Except for the objective to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age, the other immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 neutralizing titers, full-length S-binding or S1-binding IgG levels, and/or RBD-binding IgG levels (Phase 1 only) at the various time points.

1.2. Schema



Abbreviation: IRC = internal review committee.

Note: Participants ⩾16 years of age who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal), the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b1 or BNT162b2 (at any dose level) will continue in the study as originally planned.

All other participants (ie, those who were not eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations), at the approximate time participants in Phase 2/3 reach Visit 4, will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[c]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~20 mL	~20 mL	~20 mL		~20 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X								
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X											

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Provide thermometer and measuring device		X			X								
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		←	→	←	→								
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application											X		

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant ≥16 years of age becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal), the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b2 or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b2 will continue in the study as originally planned.

All other participants ≥16 years of age (ie, those who were not eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations) will be asked at Visit 4 if they wish to receive BNT162b2 if they originally received placebo prior to unblinding. If they want to receive BNT162b2, they will be unblinded and those who did originally receive placebo will move to the SoA in Section 1.3.3 for their remaining visits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X		
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL		~20 mL/ ~10 mL
Obtain nasal (midturbinate) swab	X	X					X	
Obtain randomization number and study intervention allocation	X							
Administer study intervention	X	X						

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	◄►	◄►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X	X[f]
According to eligibility, ascertain willingness to receive BNT162b2 if originally received placebo; if willing, unblind the participant's study intervention assignment (if not already done), and move placebo recipients to the SoA in Section 1.3.3			X ◄►	X				
Collect e-diary or assist the participant to delete application						X		

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants ≥16 years of age who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations (detailed separately, and available in the electronic study reference portal) will have the opportunity to receive BNT162b2 as part of the study. Any placebo recipient ≥16 years of age who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity from 6 months after Vaccination 2.

Visit Number	101	102	103	104	105	Unplanned	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm participant meets local/national recommending criteria or is at least 175 days after Vaccination 2 (Visit 4/Visit 2)	X						
Obtain informed consent	X						
Confirm participant originally received placebo	X						
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X					
Collect prohibited medication use	X	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X		
Confirm eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment	~20 mL						~20 mL
Obtain nasal (midturbinate) swab	X	X				X	
Obtain vaccine vial allocation via IRT	X	X					
Administer BNT162b2	X	X					

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	101	102	103	104	105	Unplanned	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Collect AEs and SAEs as appropriate	X	X	X	X		X[d]	X[d]
Contact the participant by telephone			X	X	X		
Request the participant return the e-diary or assist the participant to delete the application					X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)						X	X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

a. For participants who become eligible according to local/national recommendations (detailed separately, and available in the electronic study reference portal).
b. For all other Phase 2/3 placebo recipients who wish to receive BNT162b2; may be combined with Visit 4 for Phase 2/3 participants.
c. Only if the participant has no blood sample collected in the previous 7 days.
d. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.4. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4 or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner.

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

Visit Number	201	202 Onward
Visit Description	**Asymptomatic SARS-CoV-2 Infection Surveillance Consent**	**Asymptomatic SARS-CoV-2 Infection Surveillance Swab**
Visit Window (Days)	**From Approval of Protocol Amendment 11**	**Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection**
Obtain informed consent for asymptomatic SARS-CoV-2 infection surveillance	X	
Collect prohibited medication use	X	
Collect blood sample for immunogenicity assessment[a]	~20 mL/~10 mL	
Obtain nasal (midturbinate) swab (self-swab at home or by site staff at an in-person visit)	X	X
Collect AEs and SAEs as appropriate[b]	X	

a. Only if the participant has no blood sample collected in the previous 7 days. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
b. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Two SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2-mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein-receptor binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding P2 S.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with the currently available

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.

- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.

- All participants 12 to 15 years of age will be included in the reactogenicity subset (see Section 8.2.2).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of an efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Objectives[a]	Estimands	Endpoints
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19 prior to 1 month after receipt of the second dose	In participants complying with the key protocol criteria (evaluable participants) 1 month after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 prior to 1 month after receipt of the second dose
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 through the blinded follow-up period in participants without evidence of infection or confirmed COVID-19 during the study	In participants complying with the key protocol criteria (evaluable participants) 6 months after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 at initial randomization 6, 12, and 24 months after receipt of the second dose of study intervention: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for description of the manufacturing process.

Up until the final efficacy analysis, this protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
- Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination

- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal) will have the opportunity to receive BNT162b2 as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity at the approximate time participants in Phase 2/3 reach Visit 4.

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 280 participants from each of the 2 age groups

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

(12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Participants ≥16 years of age who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal) will have the opportunity to receive BNT162b2 as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 2/3 placebo recipient ≥16 years of age who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity from 6 months after Vaccination 2 (at the time of the originally planned Visit 4).

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.4. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization. Note that participants <18 years of age cannot be enrolled in the EU.

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

Informed Consent:

5. Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the study intervention(s).Receipt of medications intended to prevent COVID-19.

4. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.

5. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

   - Hypertension

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Diabetes mellitus
- Chronic pulmonary disease
- Asthma
- Current vaping or smoking
- History of chronic smoking within the prior year
- Chronic liver disease
- Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
- Resident in a long-term facility
- BMI >30 kg/m^2
- Anticipating the need for immunosuppressive treatment within the next 6 months

6. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

7. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

8. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

9. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

10. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

11. Previous vaccination with any coronavirus vaccine.

12. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

13. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

14. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

15. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

16. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

17. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

18. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

19. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

20. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

21. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Sore throat;
- Diarrhea;
- Vomiting.

2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.

3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 2 investigational RNA vaccine candidates, with the addition of saline placebo, are the 3 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	10-, 20-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. Participants ≥16 years of age who originally received placebo and accept the offer to receive BNT162b2 at defined points as part of the study will

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emea.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

receive 1 dose of BNT162b2 at each additional vaccination visit (Visits 101 and 102) in accordance with the study's additional SoA (Section 1.3.3). The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

9. Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

To allow administration of BNT162b2 to participants who originally received placebo, site staff will be unblinded to individual participants' original study intervention allocation as the participants become eligible for vaccination under local/national recommendations or from 6 months after the second dose.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).

- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

- After the formal data release of the final efficacy analysis of at least 164 cases, which is considered the primary completion of the study efficacy objectives, additional statisticians and programmers will become unblinded at the participant level to prepare unblinded analyses and other regulatory activities. A group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study.

- After the study data used for submission become public, the blinded study team will also have access to those data, and become unblinded at a group level.

- When a participant who originally received placebo receives BNT162b2 per the SoA in Section 1.3.3, the study team will become unblinded to the participant's original study intervention allocation.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

Instructions on how to unblind participants ahead of administration of BNT162b2 to placebo recipients will be provided separately: this unblinding will NOT be performed in the IRT.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).
- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.
- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants).

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, due to a medication error, a participant receives 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa), the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. In this situation:

- Obtain informed consent for administration of the additional dose.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s).

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms does not meet exclusion criterion 5 and should not result in discontinuation of study intervention, whereas a COVID-19 diagnosis does meet exclusion criterion 5 and should result in discontinuation of study intervention (see Section 8.15).

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately up to: 515 mL for participants in Phase 1, 110 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum. Additionally, 20 mL of blood for participants ≥16 years of age and 10 mL for participants in the 12- to 15-year age stratum will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 700 mL during the 24-month study period. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

period, either at the central laboratory or at a local testing facility (using an acceptable test):

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction*;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Admission to an ICU;
- Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay
- Full-length S-binding or S1-binding IgG level assay
- RBD-binding IgG level assay (Phase 1 only)
- N-binding antibody assay

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

development of other products, and/or for vaccine related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

8.1.2. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.4.

The nasal swabs will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2. For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with Section 8.3.2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Certain participants will be required to complete a reactogenicity e-diary through an application (see Section 8.1.4) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. In addition, participants 16 through 17 years of age enrolled under protocol amendment 9 and onwards will be included in the reactogenicity subset. All other participants, including those who originally received placebo and then received BNT162b2 under protocol amendment 10 and onwards, will not complete a reactogenicity e-diary but will have their local reactions and systemic events detected and reported as AEs in accordance with Section 8.3.2.

The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the last dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Additionally, for those participants who originally received placebo but go on to receive BNT162b2 at Vaccinations 3 and 4, AEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) through and including Visit 103. SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) to approximately 6 months after the second dose of BNT162b2 (Visit 104).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

Unless stated otherwise, all study visits are intended to be conducted in person at the study site. If this is not possible, because of local circumstances related to the COVID-19 pandemic, study procedures that do not require in-person participant contact may be performed by telehealth. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Irrespective of the nature of the contact, all visit procedures are expected to be performed on the same day.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Between Visits 8 and 9

All participants who have not already been unblinded, at the approximate time participants in Phase 2/3 reach Visit 4, will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, he or she will move to the procedures in Section 8.16.

8.11.1.11. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

8.11.1.12. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.

- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
    - Severe pain at the injection site.
    - Any severe systemic event.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.

- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- If Visit 3 is being conducted under amendment 10 onward: If the participant is ≥16 years of age, and is eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal), determine if he/she is willing to receive BNT162b2 as part of the study. If so, unblind the participant's study intervention assignment, and move placebo recipients to the procedures in Section 8.16.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- If not already unblinded, unblind the participant's study intervention assignment, and move placebo recipients willing to receive BNT162b2 to the procedures in Section 8.16.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;

- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;

- Fever;

- New or increased cough;

- New or increased shortness of breath;

- Chills;

- New or increased muscle pain;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
  - Symptoms and signs, including
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
    - Significant acute renal, hepatic, or neurologic dysfunction

This document cannot be used to support an marketing authorisation application and any extensions or variations thereof
pfizer.com/pharma.clinical.pd.et
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

  - Clinical diagnosis
  - Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.
  - Full blood count
  - Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
  - Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
  - Number and type of any healthcare contact; duration of hospitalization and ICU stay
  - Death
- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

8.15. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 or 14 days after receipt of the second dose, depending on the objective) of past SARS-CoV-2 infection.

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

- Asymptomatic SARS-CoV-2 infection surveillance visits: To determine the incidence of asymptomatic SARS-CoV-2 infection.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, asymptomatic SARS-CoV-2 infection surveillance visit swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result prior to Visit 2 should be handled as follows:

- Positive SARS-CoV-2 test with no symptoms, either at Visit 1 or any time between Visit 1 and Visit 2: A positive test in an asymptomatic participant does not meet exclusion criterion 5; therefore, Vaccination 2 should proceed as normal.

- Confirmed COVID-19 (ie, symptoms and positive SARS-CoV-2 test): This meets exclusion criterion 5; therefore, Vaccination 2 should not be given but the participant should remain in the study.

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

If a participant ≥16 years of age becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal), the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study.

Placebo recipients ≥16 years of age who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity from 6 months after Dose 2, and will follow the procedures listed in this section for the remainder of their participation in the study. For Phase 2/3 participants, Visit 101 could occur at the same time as the original Visit 4.

8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant originally received only placebo at Vaccination 1/2. Secondary confirmation by another site staff member is required.
- If the participant is receiving BNT162b2 following local/national recommendations, ensure he or she meets the recommending criteria (detailed separately, and available in the electronic study reference portal) OR ensure the participant is at least 175 days from Vaccination 2 (Visit 4/Visit 2, depending on the phase of the study).
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Ensure and document that inclusion criteria 2, 3, and 5 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 4 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101)

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Record AEs as described in Section 8.3.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that inclusion criteria 2, 3, and 5 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record AEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu/
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Record SAEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 103 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 104 (if any).
- Request the return of the participant's e-diary or assist the participant/participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Inform the participant/participant's parent(s)/legal guardian that his or her study participation has ended.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

8.17. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11 until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The surveillance will be conducted per the procedures listed below.

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

8.17.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11

Before surveillance begins and any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

The visit should be conducted only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1) and this visit should be temporarily delayed until the symptoms have resolved.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 3 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Record AEs as described in Section 8.3 (only if the participant remains in the AE reporting period; see Section 8.3.1).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Ask the participant to obtain a surveillance self-swab at home in approximately 14 days or schedule an appointment for the participant to return to collect the swab at the site. The swab should be collected only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1).

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.17.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection

This is a repeating swab collection and will be conducted approximately every 14 days until the intensive surveillance period ends.

- Participant collects a self-swab and ships it to the site for assessment at the central laboratory. The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- Complete the source documents with the swab information.

- The investigator or an authorized designee completes the CRFs with the swab information.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by all-available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either $VE_1 > 30\%$ or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

based on the lower bound of the 95% CI. VE will be demonstrated if the lower bound of the 2-sided 95% CI for VE is >20%.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority. ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2**.** If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

9.2. Sample Size Determination

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection will be assessed in Phase 2/3 participants (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT). Assuming a true VE of 70%, a total of 53 asymptomatic cases will provide approximately 90% power to conclude true VE >20%. A total of 206 cases is needed to have 90% power if the true VE is 50%. The hypothesis for asymptomatic seroconversion of

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

N-binding antibody will be tested if at least 206 cases are accrued. The hypothesis for asymptomatic infection based on central laboratory–confirmed NAAT in participants who are consented to participate in the intensive surveillance phase will be tested if at least 53 cases are accrued.

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 280 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.65	0.2	225	90.4%

Abbreviation: GMR = geometric mean ratio.
a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).
b. At 0.05 alpha level (2-sided).

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu/
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Population	Description
	determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 vaccination. 2. All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level**

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Endpoint	Statistical Analysis Methods
	• Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the 16- to 25-year age group)	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and 2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Endpoint	Statistical Analysis Methods
	The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Endpoint	Statistical Analysis Methods
	• 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level after Dose 1 and after Dose 2.

9.4.2. Efficacy Analyses

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Endpoint	Statistical Analysis Methods
	in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.
Secondary	**First: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Second: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Endpoint	Statistical Analysis Methods
	Third and fourth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group **Fifth and sixth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints for COVID-19 illness according to CDC-defined symptoms will be evaluated descriptively with 95% CIs. **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days or from 14 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[9] Missing efficacy data will not be imputed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Endpoint	Statistical Analysis Methods
	The following secondary efficacy endpoints regarding asymptomatic SARS-CoV-2 infection will be evaluated based on a success criterion of the lower bound of the 2-sided 95% CI for VE being >20%. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 prior to 1 month after receipt of the second dose for the active vaccine group to the placebo group** An asymptomatic case is defined as positive N-binding antibody at a post–Dose 2 visit (eg, Visit 3, 1 month after Dose 2) in participants without serological or virological evidence of infection prior to that visit, determined by negative N-binding antibody at Visit 1 and negative NAAT at Visit 1 and Visit 2 and at the time of a potential COVID-19 illness. A secondary definition will be applied without the requirement for a negative NAAT at Visit 2. VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection per 1000 person-years of follow-up in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants without evidence of infection (up to the start of asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The analysis will be based on the evaluable efficacy population and the all-available efficacy population and will include only participants who are consented to participate in the asymptomatic surveillance and who do not have serological or virological evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period.

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
Exploratory	**Ratios of confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants without, and with and without, evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** After the primary objectives are met at the final analysis of at least 164 first primary cases, the study will continue with blinded follow-up until the participant is unblinded at the time of being eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations or at approximately Visit 4. Descriptive update of VE will be provided with additional follow-up data. VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[9] Supportive analysis of time to confirmed COVID-19 illness will be performed using the Cox proportional hazard model. Kaplan-Meier cumulative incidence curves will be provided. Participants who were randomized to placebo will be censored at the time of receipt of BNT162b2. **Incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness from 7 days after the second dose will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted. **Ratio of asymptomatic SARS-CoV-2 infection through the blinded follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection in the active vaccine group to the

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. **Incidence of asymptomatic SARS-CoV-2 infection through the entire study follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants who received BNT162b2 and who have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for asymptomatic infection will be provided for participants who received BNT162b2 at initial randomization and subsequently have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with evidence of infection (up to the start of the asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. Participants who are consented to participate in the asymptomatic surveillance and who have serological or virologic evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period will be included in the analysis.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Endpoint	Statistical Analysis Methods
	For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group. AEs and SAEs reported during the open-label follow-up period will be summarized separately for participants who were unblinded at the time of being eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations or at approximately Visit 4.

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
Pfizer Inc. supplied

Endpoint	Statistical Analysis Methods
	The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory	N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" and each lot of "Process 2" will be summarized descriptively. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected randomly for the analysis.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive PPOS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 6 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu/conditional-marketing-authorisation
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8, for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall Type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

Only the first primary endpoint will be analyzed at IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints (confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and in all participants, confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection and in all participants) will be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

evaluated sequentially in the stated order, by the same method used for the evaluation of primary VE endpoints. Success thresholds for secondary VE endpoints will be appropriately chosen to control overall Type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data (with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.
- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.
- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.
- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2.
- Analysis of efficacy against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) when a sufficient number of cases have accrued to evaluate the objective(s).
- Complete safety and efficacy analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.
- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met
- Review of safety and/or immunogenicity data to:
    - Allow groups of participants of 65 to 85 years of age to proceed
    - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review
- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
    - Whether any groups may not be started
    - Whether any groups may be terminated early
    - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Up until the final efficacy analysis, 3 blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial. When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

This document cannot be used to support any marketing authorisation application in the European Economic Area and any extensions or variations thereof

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. • Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Abbreviation	Term
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
non-S	nonspike protein
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Abbreviation	Term
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs after accrual of at least 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.

4 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

5 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

6 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

7 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

8 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

9 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

10 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 11 Clean Copy, 04 Jan 2021
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	04-Jan-2021 13:54:20	Business Line Approver
PPD	04-Jan-2021 14:17:35	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195ed4f5e\Approved\Approved On: 04-Jan-2021 14:17 (GMT)

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 10	01 December 2020	• Added the possibility of administering BNT162b2 to participants who originally received placebo, following any local or national recommendations. • Added the possibility of administering BNT162b2 to participants who originally received placebo, following completion of the active safety surveillance period. • Added corresponding exploratory objectives and statistical analysis details. • Removed immunogenicity analyses of titers greater than defined threshold(s). • Removed the need for blinded COVID-19 case review after the final efficacy analysis. • Included the possibility, due to local circumstances related to the COVID-19 pandemic, that study procedures that do not require in-person participant contact may be performed by telehealth. • In light of additional information to better estimate the standard deviation of SARS-CoV-2 neutralizing titers, increased the sample size for the noninferiority immunogenicity analysis in adolescents 12 to 15 years of age.
Protocol amendment 9	29 October 2020	• To better align with the natural history of SARS-CoV-2 infection, added Phase 2/3 secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days after the second dose; also modified the existing secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days, as well as 7 days, after the second dose; • Made corresponding changes to the study design, study assessments and procedures, and statistical analysis sections. • For operational reasons, removed the interim analysis planned after accrual of 32 cases. • Clarified that interim analyses will be conducted after accrual of *at least* 62, 92, and 120 cases. • Included any participants 16 through 17 years of age enrolled under this amendment in the reactogenicity subset. • Added an unblinded clinical scientist to support DMC activities. • Clarified that serology data after a postbaseline positive SARS-CoV-2 test result will not be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		included in the analysis based on the evaluable immunogenicity populations.
Protocol amendment 8	15 October 2020	• Removed "N-binding antibody" and "SARS-CoV-2 detection by NAAT" as endpoints from the third exploratory objective, as these results are used for the determination of the population, and are not endpoints. • Clarified that the "Process 1" participants included in the descriptive analysis of "Process 1"- and "Process 2"-manufactured study interventions will be selected randomly. • Clarified that surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study. • Further modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Clarified that for participants who are not in the reactogenicity subset, local reactions and systemic events following vaccination should be detected and reported as AEs. • Clarified that premenarchal females are not WOCBP. • Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2. • Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2." • Clarified the degree of unblinding on the unblinded submissions team in Section 6.3.3. • Made provision for a second dose of BNT162b2 in participants who were affected by a medication error at Visit 2 in Section 6.6. • Provided further clarification regarding discontinuation of study intervention in Section 7.1.

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Added that 2 periods of potential COVID-19 symptoms within 4 days will be considered as a single illness. • Provided guidance in Section 8.13 regarding circumstances in which a SARS-CoV-2 test might be required even if symptoms within 7 days following each vaccination are considered more likely due to vaccine reactogenicity. • Made allowance in Section 8.13 for a second SARS-CoV-2 test to be performed within the same potential COVID-19 illness if it is in accordance with routine practice. • Added Section 8.15 to describe the reporting of SARS-CoV-2 test results and their implications for participants receiving a second vaccine dose. • Added statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age. • Amended scope of analyses of safety data in Section 9.5.1. • Made various editorial changes.
Protocol amendment 6 (Germany-specific)	23 September 2020	• According to regulatory request, inclusion criterion 1 now specifies that participants less than 18 years of age will not be enrolled in the EU.
Protocol amendment 6	08 September 2020	• Reordered some procedures in the Phase 2/3 schedule of activities for consistency with the main body of the protocol. • Corrected the window for the 6-month follow-up visit to be approximately 6 months after Vaccination 2. • Reduced the volume of blood draws to ~20 mL. • Removed the need to have safety data reported for participants to be included in the safety objective assessment. • Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease. • Increased the sample size for Phase 2/3 to ~43,998. • Clarified that inclusion criterion 4 (ie, participants at higher risk for acquiring COVID-19) is applicable for Phase 2/3 only, and provided some examples.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Removed exclusion criterion 2 (ie, known infection with HIV, HCV, or HBV) for Phase 3 and added criteria for HIV-positive participants. • Decreased the lower age limit and removed the upper age limit for inclusion in Phase 2/3 in order to evaluate BNT162b2 30 µg in older adolescents and those over 85 years of age; updated the title and other references to adults to align with this change. • Renamed the immunological assays to align with other program-level documents. • Removed reference to the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) being "heads up." • Clarified that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention. • Added clarification that potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. • Updated the analysis population descriptions to align with the study SAP.
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7. • Updated the stopping and alert rule parameters for enhanced COVID-19.
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation, and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol. • To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial • Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 17
1. PROTOCOL SUMMARY 18
1.1. Synopsis 18
1.2. Schema 26
1.3. Schedule of Activities 27
1.3.1. Phase 1 27
1.3.2. Phase 2/3 33
1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo 37
2. INTRODUCTION 39
2.1. Study Rationale 39
2.2. Background 39
2.2.1. Clinical Overview 40
2.3. Benefit/Risk Assessment 40
2.3.1. Risk Assessment 42
2.3.2. Benefit Assessment 44
2.3.3. Overall Benefit/Risk Conclusion 44
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 44
3.1. For Phase 1 44
3.2. For Phase 2/3 46
4. STUDY DESIGN 49
4.1. Overall Design 49
4.1.1. Phase 1 50
4.1.2. Phase 2/3 51
4.2. Scientific Rationale for Study Design 52
4.3. Justification for Dose 53
4.4. End of Study Definition 54
5. STUDY POPULATION 54
5.1. Inclusion Criteria 54
5.2. Exclusion Criteria 55
5.3. Lifestyle Considerations 57

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

5.3.1. Contraception 57
5.4. Screen Failures 58
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 58
6. STUDY INTERVENTION 59
6.1. Study Intervention(s) Administered 59
6.1.1. Manufacturing Process 60
6.1.2. Administration 60
6.2. Preparation/Handling/Storage/Accountability 61
6.2.1. Preparation and Dispensing 62
6.3. Measures to Minimize Bias: Randomization and Blinding 62
6.3.1. Allocation to Study Intervention 62
6.3.2. Blinding of Site Personnel 62
6.3.3. Blinding of the Sponsor 63
6.3.4. Breaking the Blind 64
6.4. Study Intervention Compliance 64
6.5. Concomitant Therapy 64
6.5.1. Prohibited During the Study 65
6.5.2. Permitted During the Study 65
6.6. Dose Modification 66
6.7. Intervention After the End of the Study 66
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 67
7.1. Discontinuation of Study Intervention 67
7.2. Participant Discontinuation/Withdrawal From the Study 67
7.2.1. Withdrawal of Consent 68
7.3. Lost to Follow-up 68
8. STUDY ASSESSMENTS AND PROCEDURES 69
8.1. Efficacy and/or Immunogenicity Assessments 70
8.1.1. Biological Samples 72
8.2. Safety Assessments 73
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 73

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

8.2.2. Electronic Diary 74
8.2.2.1. Grading Scales 74
8.2.2.2. Local Reactions 75
8.2.2.3. Systemic Events 75
8.2.2.4. Fever 76
8.2.2.5. Antipyretic Medication 77
8.2.3. Phase 1 Stopping Rules 77
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 78
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 79
8.2.6. Pregnancy Testing 79
8.3. Adverse Events and Serious Adverse Events 79
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 80
8.3.1.1. Reporting SAEs to Pfizer Safety 81
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 81
8.3.2. Method of Detecting AEs and SAEs 81
8.3.3. Follow-up of AEs and SAEs 81
8.3.4. Regulatory Reporting Requirements for SAEs 81
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 82
8.3.5.1. Exposure During Pregnancy 82
8.3.5.2. Exposure During Breastfeeding 84
8.3.5.3. Occupational Exposure 84
8.3.6. Cardiovascular and Death Events 84
8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 85
8.3.8. Adverse Events of Special Interest 85
8.3.8.1. Lack of Efficacy 85
8.3.9. Medical Device Deficiencies 85
8.3.10. Medication Errors 85
8.4. Treatment of Overdose 86
8.5. Pharmacokinetics 87

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.6. Pharmacodynamics 87
8.7. Genetics 87
8.8. Biomarkers 87
8.9. Immunogenicity Assessments 87
8.10. Health Economics 87
8.11. Study Procedures 87
8.11.1. Phase 1 88
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 88
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 89
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 91
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 92
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 93
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 96
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 97
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 98
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4) 99
8.11.1.10. Between Visits 8 and 9 99
8.11.1.11. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2 99
8.11.1.12. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2 100
8.11.2. Phase 2/3 100
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 100
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 103

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2) 105
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2) 106
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 107
8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2 107
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 108
8.13. COVID-19 Surveillance (All Participants) 109
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 110
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit) 111
8.14. Communication and Use of Technology 112
8.15. SARS-CoV-2 NAAT Results From Visits 1 and 2 and Potential COVID-19 Illness Visits 113
8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo 113
8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2) 114
8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101) 115
8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102) 116
8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102) 117
8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102) 117
9. STATISTICAL CONSIDERATIONS 118
9.1. Estimands and Statistical Hypotheses 118
9.1.1. Estimands 118
9.1.2. Statistical Hypotheses 118

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy....118
9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity....119
9.2. Sample Size Determination....119
9.3. Analysis Sets....121
9.4. Statistical Analyses....121
9.4.1. Immunogenicity Analyses....122
9.4.2. Efficacy Analyses....126
9.4.3. Safety Analyses....129
9.4.4. Other Analyses....130
9.5. Interim Analyses....131
9.5.1. Analysis Timing....134
9.6. Data Monitoring Committee or Other Independent Oversight Committee....134
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS....136
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations....136
10.1.1. Regulatory and Ethical Considerations....136
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP....136
10.1.2. Informed Consent Process....137
10.1.3. Data Protection....138
10.1.4. Dissemination of Clinical Study Data....138
10.1.5. Data Quality Assurance....139
10.1.6. Source Documents....141
10.1.7. Study and Site Start and Closure....141
10.1.8. Sponsor's Qualified Medical Personnel....142
10.2. Appendix 2: Clinical Laboratory Tests....143
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting....145
10.3.1. Definition of AE....145
10.3.2. Definition of SAE....146
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs....148
10.3.4. Reporting of SAEs....151

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

10.4. Appendix 4: Contraceptive Guidance 152
10.4.1. Male Participant Reproductive Inclusion Criteria 152
10.4.2. Female Participant Reproductive Inclusion Criteria....152
10.4.3. Woman of Childbearing Potential 153
10.4.4. Contraception Methods....154
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 156
10.6. Appendix 6: Abbreviations 158
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 162
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection 165
11. REFERENCES 166

LIST OF TABLES

Table 1. Local Reaction Grading Scale 75
Table 2. Systemic Event Grading Scale....76
Table 3. Scale for Fever....77
Table 4. Power Analysis for Noninferiority Assessment 120
Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 120
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility....132
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses....132
Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall....133
Table 9. Laboratory Abnormality Grading Scale 143
Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 163
Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 164

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and efficacy of these prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Objectives[a]	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in <u>all participants</u> randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: ○ Local reactions (pain at the injection site, redness, and swelling) ○ Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100× (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• N-binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for a description of the manufacturing process.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants ≥16 years of age who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

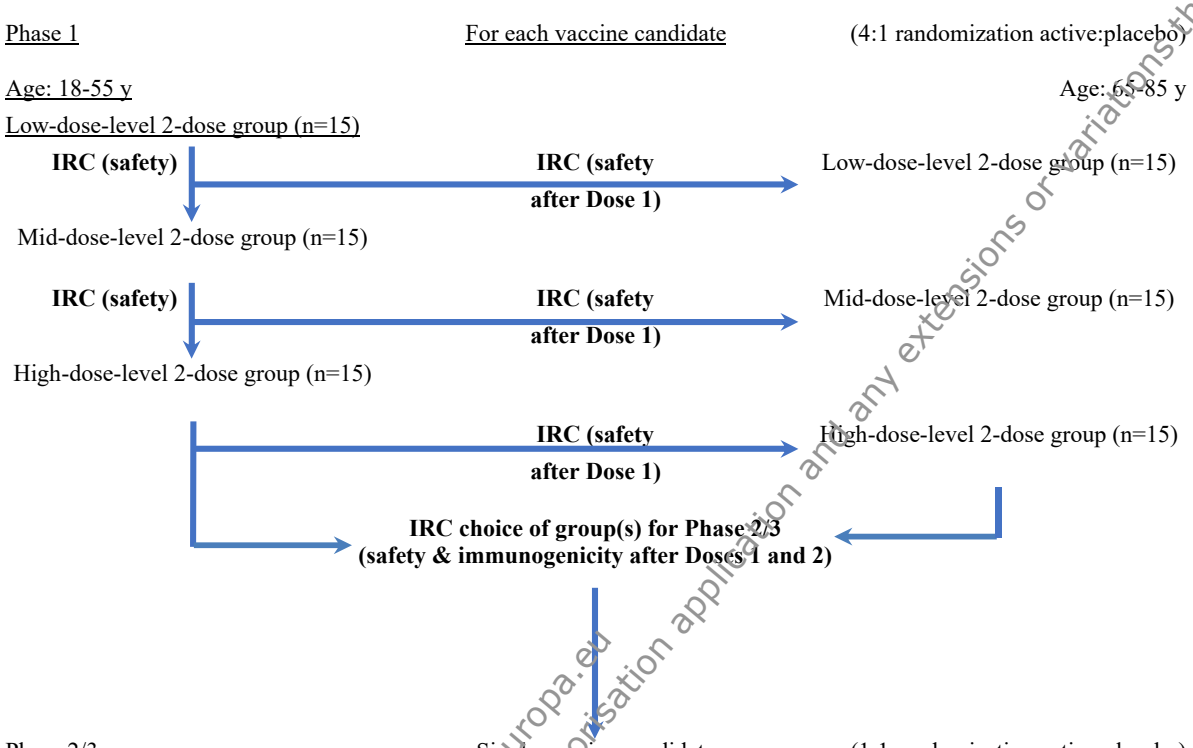
In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

Except for the objective to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age, the other immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and/or RBD-binding IgG levels at the various time points.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

1.2. Schema



Abbreviation: IRC = internal review committee.

Note: Participants ⩾16 years of age who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal), the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b1 or BNT162b2 (at any dose level) will continue in the study as originally planned.

All other participants (ie, those who were not eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations), at the approximate time participants in Phase 2/3 reach Visit 4, will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[c]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~20 mL	~20 mL	~20 mL		~20 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X								
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X											

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Provide thermometer and measuring device		X			X								
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		←	→		←	→							
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application											X		

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant ≥16 years of age becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal), the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b2 or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b2 will continue in the study as originally planned.

All other participants ≥16 years of age (ie, those who were not eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations) will be asked at Visit 4 if they wish to receive BNT162b2 if they originally received placebo prior to unblinding. If they want to receive BNT162b2, they will be unblinded and those who did originally receive placebo will move to the SoA in Section 1.3.3 for their remaining visits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X		
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL		~20 mL/ ~10 mL
Obtain nasal (midturbinate) swab	X	X					X	
Obtain randomization number and study intervention allocation	X							
Administer study intervention	X	X						

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	◄►	◄►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X	X[f]
According to eligibility, ascertain willingness to receive BNT162b2 if originally received placebo; if willing, unblind the participant's study intervention assignment (if not already done), and move placebo recipients to the SoA in Section 1.3.3			X ◄►	X				
Collect e-diary or assist the participant to delete application						X		

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	Vaccination 1	Vaccination 2	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit[a]	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Day 1[b]	19 to 23 Days After Visit 1	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	350 to 378 Days After Visit 2	714 to 742 Days After Visit 2	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants ≥16 years of age who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations (detailed separately, and available in the electronic study reference portal) will have the opportunity to receive BNT162b2 as part of the study. Any placebo recipient ≥16 years of age who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity from 6 months after Vaccination 2.

Visit Number	101	102	103	104	105	Unplanned	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm participant meets local/national recommending criteria or is at least 175 days after Vaccination 2 (Visit 4/Visit 2)	X						
Obtain informed consent	X						
Confirm participant originally received placebo	X						
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X					
Collect prohibited medication use	X	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X		
Confirm eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment	~20 mL						~20 mL
Obtain nasal (midturbinate) swab	X	X				X	
Obtain vaccine vial allocation via IRT	X	X					
Administer BNT162b2	X	X					

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	101	102	103	104	105	Unplanned	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Collect AEs and SAEs as appropriate	X	X	X	X		X[d]	X[d]
Contact the participant by telephone			X	X	X		
Request the participant return the e-diary or assist the participant to delete the application					X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)						X	X

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

a. For participants who become eligible according to local/national recommendations (detailed separately, and available in the electronic study reference portal).
b. For all other Phase 2/3 placebo recipients who wish to receive BNT162b2; may be combined with Visit 4 for Phase 2/3 participants.
c. Only if the participant has no blood sample collected in the previous 7 days.
d. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Two SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2-mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein-receptor binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding P2 S.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

the currently available therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.
- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.
- All participants 12 to 15 years of age will be included in the reactogenicity subset (see Section 8.2.2).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of an efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Objectives[a]	Estimands	Endpoints
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Objectives[a]	Estimands	Endpoints
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• N-binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for description of the manufacturing process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Up until the final efficacy analysis, this protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

separately, and available in the electronic study reference portal) will have the opportunity to receive BNT162b2 as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity at any point from 6 months after Vaccination 2 onwards.

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team,

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 280 participants from each of the 2 age groups (12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Participants ≥16 years of age who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal) will have the opportunity to receive BNT162b2 from 1 month after Vaccination 2 as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 2/3 placebo recipient ≥16 years of age who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity from 6 months after Vaccination 2 (at the time of the originally planned Visit 4).

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (Section 1.3.3).

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization. Note that participants <18 years of age cannot be enrolled in the EU.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

    Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants

This document can only be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

Informed Consent:

5. Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:
    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- History of chronic smoking within the prior year
- Chronic liver disease
- Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
- Resident in a long-term facility
- BMI >30 kg/m^2
- Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

This document can not be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;
    - Sore throat;
    - Diarrhea;
    - Vomiting.
2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.
3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 2 investigational RNA vaccine candidates, with the addition of saline placebo, are the 3 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	10-, 20-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. Participants ≥16 years of age who originally received placebo and accept the offer to receive BNT162b2 at defined points as part of the study will receive 1 dose of BNT162b2 at each additional vaccination visit (Visits 101 and 102) in accordance with the study's additional SoA (Section 1.3.3). The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

To allow administration of BNT162b2 to participants who originally received placebo, site staff will be unblinded to individual participants' original study intervention allocation as the participants become eligible for vaccination under local/national recommendations or from 6 months after the second dose.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).

- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

- After the formal data release of the final efficacy analysis of at least 164 cases, which is considered the primary completion of the study efficacy objectives, additional statisticians and programmers will become unblinded at the participant level to

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

prepare unblinded analyses and other regulatory activities. A group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study.

- After the study data used for submission become public, the blinded study team will also have access to those data, and become unblinded at a group level.

- When a participant who originally received placebo receives BNT162b2 per the SoA in Section 1.3.3, the study team will become unblinded to the participant's original study intervention allocation.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

Instructions on how to unblind participants ahead of administration of BNT162b2 to placebo recipients will be provided separately: this unblinding will NOT be performed in the IRT.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants).

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, due to a medication error, a participant receives 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa), the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. In this situation:

- Obtain informed consent for administration of the additional dose.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s).

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms does not meet exclusion criterion 5 and should not result in discontinuation of study intervention, whereas a COVID-19 diagnosis does meet exclusion criterion 5 and should result in discontinuation of study intervention (see Section 8.15).

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately up to: 515 mL for participants in Phase 1, 110 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum. Additionally, 20 mL of blood for participants ≥16 years of age and 10 mL for participants in the 12- to 15-year age stratum

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 700 mL during the 24-month study period. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
  - Fever;
  - New or increased cough;
  - New or increased shortness of breath;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction*;
  - Admission to an ICU;
  - Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay
- S1-binding IgG level assay
- RBD-binding IgG level assay
- N-binding antibody assay

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2. For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with Section 8.3.2.

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Certain participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. In addition, participants 16 through 17 years of age enrolled under protocol amendment 9 and onwards will be included in the reactogenicity subset. All other participants, including those who originally received placebo and then received BNT162b2 under protocol amendment 10 and onwards, will not complete a reactogenicity e-diary but will have their local reactions and systemic events detected and reported as AEs in accordance with Section 8.3.2.

The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the last dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeurope.ru
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Additionally, for those participants who originally received placebo but go on to receive BNT162b2 at Vaccinations 3 and 4, AEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) through and including Visit 103. SAEs will be collected from the time the participant provides informed consent (for receipt of Vaccinations 3 and 4) to approximately 6 months after the second dose of BNT162b2 (Visit 104).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

This document cannot be used to support any marketing authorisation application and/or extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

Unless stated otherwise, all study visits are intended to be conducted in person at the study site. If this is not possible, because of local circumstances related to the COVID-19 pandemic, study procedures that do not require in-person participant contact may be performed by telehealth. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Irrespective of the nature of the contact, all visit procedures are expected to be performed on the same day.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

- Fever ≥39.0°C (≥102.1°F).
- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.1.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

(including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Between Visits 8 and 9

All participants who have not already been unblinded, at the approximate time participants in Phase 2/3 reach Visit 4, will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, he or she will move to the procedures in Section 8.16.

8.11.1.11. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.12. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.

    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

    - Fever ≥39.0°C (≥102.1°F).

    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

    - Severe pain at the injection site.

    - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (≥20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- If Visit 3 is being conducted under amendment 10 onward: If the participant is ≥16 years of age, and is eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal), determine if he/she is willing to receive BNT162b2 as part of the study. If so, unblind the participant's study intervention assignment, and move placebo recipients to the procedures in Section 8.16.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- If not already unblinded, unblind the participant's study intervention assignment, and move placebo recipients willing to receive BNT162b2 to the procedures in Section 8.16.

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
    - Symptoms and signs, including
        - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

- Clinical diagnosis
- Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.
- Full blood count
- Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
- Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
- Number and type of any healthcare contact; duration of hospitalization and ICU stay
- Death

- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

8.15. SARS-CoV-2 NAAT Results From Visits 1 and 2 and Potential COVID-19 Illness Visits

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 or 14 days after receipt of the second dose, depending on the objective) of past SARS-CoV-2 infection.

- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result prior to Visit 2 should be handled as follows:

- Positive SARS-CoV-2 test with no symptoms, either at Visit 1 or any time between Visit 1 and Visit 2: A positive test in an asymptomatic participant does not meet exclusion criterion 5; therefore, Vaccination 2 should proceed as normal.

- Confirmed COVID-19 (ie, symptoms and positive SARS-CoV-2 test): This meets exclusion criterion 5; therefore, Vaccination 2 should not be given but the participant should remain in the study.

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

If a participant ≥16 years of age becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal), the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study.

Placebo recipients ≥16 years of age who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity from 6 months after Dose 2, and will follow the procedures listed in this section for the remainder of their participation in the study. For Phase 2/3 participants, Visit 101 could occur at the same time as the original Visit 4.

This document cannot be used to support an marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant originally received only placebo at Vaccination 1/2. Secondary confirmation by another site staff member is required.
- If the participant is receiving BNT162b2 following local/national recommendations, ensure he or she meets the recommending criteria (detailed separately, and available in the electronic study reference portal) OR ensure the participant is at least 175 days from Vaccination 2 (Visit 4/Visit 2, depending on the phase of the study).
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Ensure and document that inclusion criteria 2, 3, and 5 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 4 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101)

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Record AEs as described in Section 8.3.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

- Discuss contraceptive use as described in Section 10.4.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Ensure and document that inclusion criteria 2, 3, and 5 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Obtain a nasal (midturbinate) swab (collected by site staff).

- Obtain the participant's vaccine vial allocation using the IRT system.

- Site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment to call the participant by telephone for the next study contact.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.

- Record AEs as described in Section 8.3.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment to call the participant by telephone for the next study contact.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 103 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 104 (if any).
- Request the return of the participant's e-diary or assist the participant/participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Inform the participant/participant's parent(s)/legal guardian that his or her study participation has ended.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- The investigator or an authorized designee completes the CRFs.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by all-available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either VE_1 >30% or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2**.** If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

9.2. Sample Size Determination

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 280 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

below, a sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.65	-0.2	225	90.4%

Abbreviation: GMR = geometric mean ratio.
a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).
b. At 0.05 alpha level (2-sided).

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 vaccination. 2. All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Endpoint	Statistical Analysis Methods
	GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the 16- to 25-year age group)	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and 2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment. The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Endpoint	Statistical Analysis Methods
	• 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with the immune response (non-S) to SARS-CoV-2 for N-binding antibody at the time points when data are available** The Clopper-Pearson method will be used to calculate the CIs. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Endpoint	Statistical Analysis Methods
	summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level after Dose 1 and after Dose 2.

9.4.2. Efficacy Analyses

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.
Secondary	**First: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Second: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Third and fourth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Fifth and sixth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Endpoint	Statistical Analysis Methods
	The following secondary efficacy endpoints will be evaluated descriptively with 95% CIs. **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days or from 14 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[9] Missing efficacy data will not be imputed.
Exploratory	**Ratios of confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants without, and with and without, evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** After the primary objectives are met at the final analysis of at least 164 first primary cases, the study will continue with blinded follow-up until the participant is unblinded at the time of being eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations or at approximately Visit 4. Descriptive update of VE will be provided with additional follow-up data. VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[9] Supportive analysis of time to confirmed COVID-19 illness will be performed using the Cox proportional hazard model. Kaplan-Meier cumulative incidence curves will be provided. Participants who were

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Endpoint	Statistical Analysis Methods
	randomized to placebo will be censored at the time of receipt of BNT162b2. **Incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness from 7 days after the second dose will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Endpoint	Statistical Analysis Methods
	are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group. The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory	N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" and each lot of "Process 2" will be summarized descriptively. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected randomly for the analysis.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 6 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8, for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall Type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

Only the first primary endpoint will be analyzed at IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints (confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and in all participants, confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection and in all participants) will be evaluated sequentially in the stated order, by the same method used for the evaluation of primary VE endpoints. Success thresholds for secondary VE endpoints will be appropriately chosen to control overall Type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data (with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.
- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.
- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.
- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2.
- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.
- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Review of safety and/or immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review
- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Up until the final efficacy analysis, 3 blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. • Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.
- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
non-S	nonspike protein
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Abbreviation	Term
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs after accrual of at least 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.

4 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

5 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

6 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

7 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

8 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

9 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

10 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

Document Approval Record

Document Name:	C4591001, Clinical Protocol Amendment 10, Clean Copy, 01Dec2020
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	01-Dec-2020 21:56:47	Business Line Approver
PPD	01-Dec-2020 23:02:48	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195aa1db5\Approved\Approved On: 01-Dec-2020 23:02 (GMT)

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 9	29 October 2020	• To better align with the natural history of SARS-CoV-2 infection, added Phase 2/3 secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days after the second dose; also modified the existing secondary efficacy objectives, estimands, and endpoints to include COVID-19 cases that occur from 14 days, as well as 7 days, after the second dose; • Made corresponding changes to the study design, study assessments and procedures, and statistical analysis sections. • For operational reasons, removed the interim analysis planned after accrual of 32 cases. • Clarified that interim analyses will be conducted after accrual of *at least* 62, 92, and 120 cases. • Included any participants 16 through 17 years of age enrolled under this amendment in the reactogenicity subset. • Added an unblinded clinical scientist to support DMC activities. • Clarified that serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.
Protocol amendment 8	15 October 2020	• Removed “N-binding antibody” and “SARS-CoV-2 detection by NAAT” as endpoints from the third exploratory objective, as these results are used for the determination of the population, and are not endpoints. • Clarified that the “Process 1” participants included in the descriptive analysis of “Process 1”- and “Process 2”-manufactured study interventions will be selected randomly. • Clarified that surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study. • Further modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Clarified that for participants who are not in the reactogenicity subset, local reactions and systemic events following vaccination should be detected and reported as AEs. • Clarified that premenarchal females are not WOCBP.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2. • Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2." • Clarified the degree of unblinding on the unblinded submissions team in Section 6.3.3. • Made provision for a second dose of BNT162b2 in participants who were affected by a medication error at Visit 2 in Section 6.6. • Provided further clarification regarding discontinuation of study intervention in Section 7.1. • Modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Added that 2 periods of potential COVID-19 symptoms within 4 days will be considered as a single illness. • Provided guidance in Section 8.13 regarding circumstances in which a SARS-CoV-2 test might be required even if symptoms within 7 days following each vaccination are considered more likely due to vaccine reactogenicity. • Made allowance in Section 8.13 for a second SARS-CoV-2 test to be performed within the same potential COVID-19 illness if it is in accordance with routine practice. • Added Section 8.15 to describe the reporting of SARS-CoV-2 test results and their implications for participants receiving a second vaccine dose. • Added statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age. • Amended scope of analyses of safety data in Section 9.5.1.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Made various editorial changes.
Protocol amendment 6 (Germany-specific)	23 September 2020	• According to regulatory request, inclusion criterion 1 now specifies that participants less than 18 years of age will not be enrolled in the EU.
Protocol amendment 6	08 September 2020	• Reordered some procedures in the Phase 2/3 schedule of activities for consistency with the main body of the protocol. • Corrected the window for the 6-month follow-up visit to be approximately 6 months after Vaccination 2. • Reduced the volume of blood draws to ~20 mL. • Removed the need to have safety data reported for participants to be included in the safety objective assessment. • Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease. • Increased the sample size for Phase 2/3 to ~43,998. • Clarified that inclusion criterion 4 (ie, participants at higher risk for acquiring COVID-19) is applicable for Phase 2/3 only, and provided some examples. • Removed exclusion criterion 2 (ie, known infection with HIV, HCV, or HBV) for Phase 3 and added criteria for HIV-positive participants. • Decreased the lower age limit and removed the upper age limit for inclusion in Phase 2/3 in order to evaluate BNT162b2 30 µg in older adolescents and those over 85 years of age; updated the title and other references to adults to align with this change. • Renamed the immunological assays to align with other program-level documents. • Removed reference to the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) being “heads up.” • Clarified that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention. • Added clarification that potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. • Updated the analysis population descriptions to align with the study SAP.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory. • Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7. • Updated the stopping and alert rule parameters for enhanced COVID-19.

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 15
1. PROTOCOL SUMMARY 17
1.1. Synopsis 17
1.2. Schema 25
1.3. Schedule of Activities 26
1.3.1. Phase 1 26
1.3.2. Phase 2/3 31
2. INTRODUCTION 34
2.1. Study Rationale 34
2.2. Background 34
2.2.1. Clinical Overview 35
2.3. Benefit/Risk Assessment 35
2.3.1. Risk Assessment 37
2.3.2. Benefit Assessment 39
2.3.3. Overall Benefit/Risk Conclusion 39
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 39
3.1. For Phase 1 39
3.2. For Phase 2/3 41
4. STUDY DESIGN 44
4.1. Overall Design 44
4.1.1. Phase 1 44
4.1.2. Phase 2/3 45
4.2. Scientific Rationale for Study Design 47
4.3. Justification for Dose 47
4.4. End of Study Definition 48
5. STUDY POPULATION 48
5.1. Inclusion Criteria 48
5.2. Exclusion Criteria 49
5.3. Lifestyle Considerations 52
5.3.1. Contraception 52

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

5.4. Screen Failures 52
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 52
6. STUDY INTERVENTION 53
6.1. Study Intervention(s) Administered 54
6.1.1. Manufacturing Process 54
6.1.2. Administration 54
6.2. Preparation/Handling/Storage/Accountability 55
6.2.1. Preparation and Dispensing 56
6.3. Measures to Minimize Bias: Randomization and Blinding 56
6.3.1. Allocation to Study Intervention 56
6.3.2. Blinding of Site Personnel 56
6.3.3. Blinding of the Sponsor 57
6.3.4. Breaking the Blind 58
6.4. Study Intervention Compliance 58
6.5. Concomitant Therapy 58
6.5.1. Prohibited During the Study 58
6.5.2. Permitted During the Study 59
6.6. Dose Modification 59
6.7. Intervention After the End of the Study 60
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 60
7.1. Discontinuation of Study Intervention 60
7.2. Participant Discontinuation/Withdrawal From the Study 61
7.2.1. Withdrawal of Consent 62
7.3. Lost to Follow-up 62
8. STUDY ASSESSMENTS AND PROCEDURES 62
8.1. Efficacy and/or Immunogenicity Assessments 63
8.1.1. Biological Samples 66
8.2. Safety Assessments 66
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 67
8.2.2. Electronic Diary 67

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

8.2.2.1. Grading Scales 68
8.2.2.2. Local Reactions 68
8.2.2.3. Systemic Events 69
8.2.2.4. Fever 70
8.2.2.5. Antipyretic Medication 71
8.2.3. Phase 1 Stopping Rules 71
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 72
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 73
8.2.6. Pregnancy Testing 73
8.3. Adverse Events and Serious Adverse Events 73
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 73
8.3.1.1. Reporting SAEs to Pfizer Safety 74
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 74
8.3.2. Method of Detecting AEs and SAEs 75
8.3.3. Follow-up of AEs and SAEs 75
8.3.4. Regulatory Reporting Requirements for SAEs 75
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 75
8.3.5.1. Exposure During Pregnancy 76
8.3.5.2. Exposure During Breastfeeding 77
8.3.5.3. Occupational Exposure 78
8.3.6. Cardiovascular and Death Events 78
8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 78
8.3.8. Adverse Events of Special Interest 79
8.3.8.1. Lack of Efficacy 79
8.3.9. Medical Device Deficiencies 79
8.3.10. Medication Errors 79
8.4. Treatment of Overdose 80
8.5. Pharmacokinetics 80
8.6. Pharmacodynamics 80

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

8.7. Genetics 80
8.8. Biomarkers 81
8.9. Immunogenicity Assessments 81
8.10. Health Economics 81
8.11. Study Procedures 81
8.11.1. Phase 1 81
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 81
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 82
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 84
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 86
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 87
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 89
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 90
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 91
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4) 92
8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4) 92
8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4) 93
8.11.2. Phase 2/3 93
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 93
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 96
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2) 98
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2) 99
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2) 99

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2) 100
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 100
8.13. COVID-19 Surveillance (All Participants) 101
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 103
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit) 104
8.14. Communication and Use of Technology 105
8.15. SARS-CoV-2 NAAT Results From Visits 1 and 2 and Potential COVID-19 Illness Visits 105
9. STATISTICAL CONSIDERATIONS 106
9.1. Estimands and Statistical Hypotheses 106
9.1.1. Estimands 106
9.1.2. Statistical Hypotheses 107
9.1.2.1. Statistical Hypothesis Evaluation for Efficacy 107
9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity 107
9.2. Sample Size Determination 107
9.3. Analysis Sets 109
9.4. Statistical Analyses 110
9.4.1. Immunogenicity Analyses 110
9.4.2. Efficacy Analyses 115
9.4.3. Safety Analyses 117
9.4.4. Other Analyses 118
9.5. Interim Analyses 119
9.5.1. Analysis Timing 122
9.6. Data Monitoring Committee or Other Independent Oversight Committee 122
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 124
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 124
10.1.1. Regulatory and Ethical Considerations 124
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 124

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.1.2. Informed Consent Process 125
10.1.3. Data Protection 126
10.1.4. Dissemination of Clinical Study Data 126
10.1.5. Data Quality Assurance 127
10.1.6. Source Documents 129
10.1.7. Study and Site Start and Closure 129
10.1.8. Sponsor's Qualified Medical Personnel 130
10.2. Appendix 2: Clinical Laboratory Tests 131
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 133
10.3.1. Definition of AE 133
10.3.2. Definition of SAE 134
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 136
10.3.4. Reporting of SAEs 139
10.4. Appendix 4: Contraceptive Guidance 140
10.4.1. Male Participant Reproductive Inclusion Criteria 140
10.4.2. Female Participant Reproductive Inclusion Criteria 140
10.4.3. Woman of Childbearing Potential 141
10.4.4. Contraception Methods 142
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 144
10.6. Appendix 6: Abbreviations 146
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 150
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection 153
11. REFERENCES 154

LIST OF TABLES

Table 1. Local Reaction Grading Scale 69
Table 2. Systemic Event Grading Scale 69
Table 3. Scale for Fever 70
Table 4. Power Analysis for Noninferiority Assessment 108

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 109
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility 120
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses 121
Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall 121
Table 9. Laboratory Abnormality Grading Scale 131
Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 151
Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 152

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and efficacy of these prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Objectives[a]	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in <u>all participants</u> randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100× (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• N-binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• All safety endpoints described above • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for a description of the manufacturing process.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90%

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

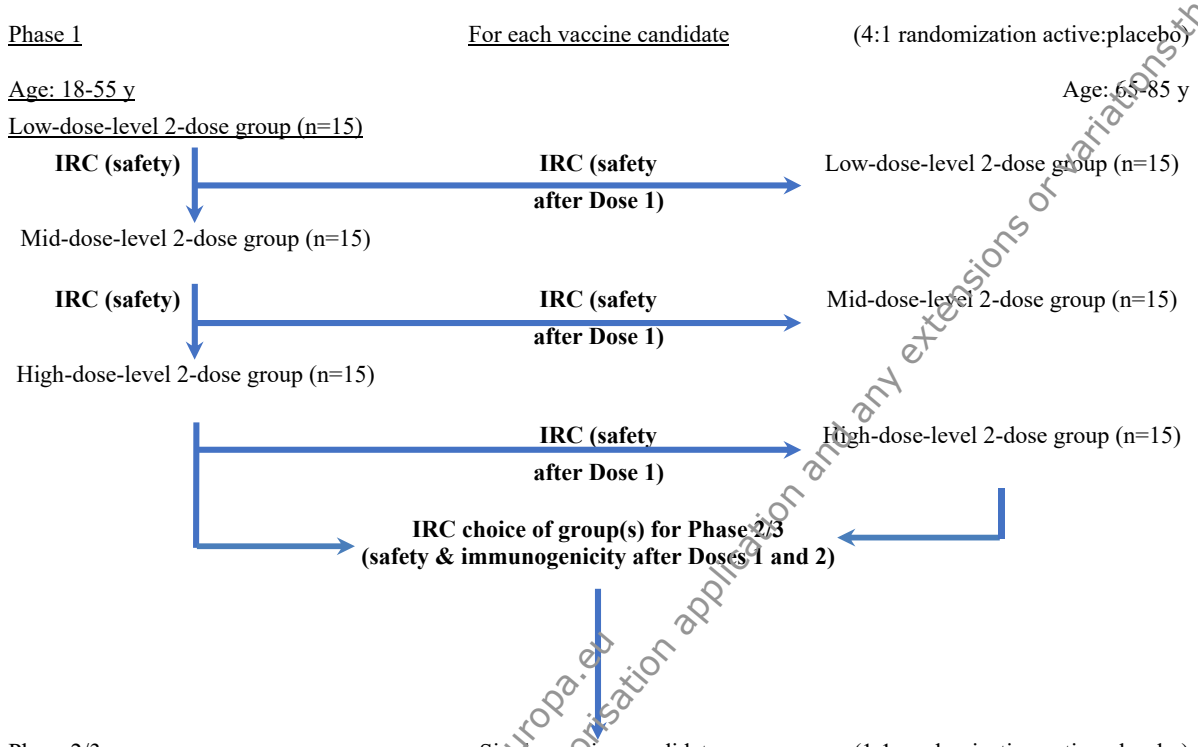
In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

Except for the objective to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age, the other immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, percentage of participants with ≥ specified threshold, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and/or RBD-binding IgG levels at the various time points.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

1.2. Schema



Abbreviation: IRC = internal review committee.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						

This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[c]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~20 mL	~20 mL	~20 mL		~20 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X								
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X											
Provide thermometer and measuring device		X			X								
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►	◄	►							

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application											X		

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C.

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X		
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL		~20 mL/ ~10 mL
Obtain nasal (midturbinate) swab	X	X					X	

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain randomization number and study intervention allocation	X							
Administer study intervention	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	◄——►	◄——►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X	X[f]
Collect e-diary or assist the participant to delete application						X		

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Two SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2-mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein-receptor binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding P2 S.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

the currently available therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.
- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.
- All participants 12 to 15 years of age will be included in the reactogenicity subset (see Section 8.2.2).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of a potentially efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Objectives[a]	Estimands	Endpoints
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Objectives[a]	Estimands	Endpoints
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• N-binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• All safety endpoints described above • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for description of the manufacturing process.

This protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1,

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 250 participants from each of the 2 age groups (12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization. Note that participants <18 years of age cannot be enrolled in the EU.

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used for supporting any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

Informed Consent:

5. Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - Chronic liver disease
    - Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
    - Resident in a long-term facility
    - BMI >30 kg/m^2
    - Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Sore throat;
- Diarrhea;
- Vomiting.

2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.

3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 2 investigational RNA vaccine candidates, with the addition of saline placebo, are the 3 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application in the european union and any extensions or variations thereof

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	10-, 20-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWRS). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel,

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).

- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).
- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.
- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants).

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, due to a medication error, a participant receives 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa), the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. In this situation:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Obtain informed consent for administration of the additional dose.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s).

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms does not meet exclusion criterion 5 and should not result in discontinuation of study intervention, whereas a COVID-19 diagnosis does meet exclusion criterion 5 and should result in discontinuation of study intervention (see Section 8.15).

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately up to: 515 mL for participants in Phase 1, 110 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum. Additionally, 20 mL of blood for participants ≥16 years of age and 10 mL for participants in the 12- to 15-year age stratum will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 700 mL during the 24-month study period. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
  - Fever;
  - New or increased cough;
  - New or increased shortness of breath;
  - Chills;
  - New or increased muscle pain;
  - New loss of taste or smell;
  - Sore throat;
  - Diarrhea;
  - Vomiting.

  The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

  - Fatigue;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Headache;
- Nasal congestion or runny nose;
- Nausea.

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction*;
  - Admission to an ICU;
  - Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- S1-binding IgG level assay
- RBD-binding IgG level assay
- N-binding antibody assay

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2. For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with Section 8.3.2.

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. In addition, participants 16 through 17 years of age enrolled under protocol amendment 9 and onwards will be included in the reactogenicity subset. The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the last dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
eu.eudra.ec
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
  - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.

This document cannot be used to support marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu/ema

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6, 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.

    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

    - Fever ≥39.0°C (≥102.1°F).

    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

    - Severe pain at the injection site.

    - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (≥20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.

- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:

  - Symptoms and signs, including

    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)

    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)

    - Significant acute renal, hepatic, or neurologic dysfunction

    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

  - Clinical diagnosis

  - Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

(midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.

- Full blood count
- Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
- Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
- Number and type of any healthcare contact; duration of hospitalization and ICU stay
- Death

- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

8.15. SARS-CoV-2 NAAT Results From Visits 1 and 2 and Potential COVID-19 Illness Visits

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 or 14 days after receipt of the second dose, depending on the objective) of past SARS-CoV-2 infection.
- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result prior to Visit 2 should be handled as follows:

- Positive SARS-CoV-2 test with no symptoms, either at Visit 1 or any time between Visit 1 and Visit 2: A positive test in an asymptomatic participant does not meet exclusion criterion 5; therefore, Vaccination 2 should proceed as normal.

- Confirmed COVID-19 (ie, symptoms and positive SARS-CoV-2 test): This meets exclusion criterion 5; therefore, Vaccination 2 should not be given but the participant should remain in the study.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by all-available efficacy population. Missing laboratory

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either $VE_1 > 30\%$ or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2**.** If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

9.2. Sample Size Determination

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 250 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.623	-0.2	200	90.8%

Abbreviation: GMR = geometric mean ratio.

a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 1, N=12). Calculation may be updated if additional information becomes available to better estimate the standard deviation.

b. At 0.05 alpha level (2-sided).

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.

This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Population	Description
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 vaccination. 2. All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Endpoint	Statistical Analysis Methods
	participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Endpoint	Statistical Analysis Methods
16- to 25-year age group)	2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment. The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3:

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	• 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with antibody levels ≥ predefined threshold(s) for SARS-CoV-2 serological parameters** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels and/or RBD-binding IgG levels, N-binding antibody, and SARS-CoV-2 detection by NAAT, percentages (and 2-sided 95% CIs) of participants with antibody levels ≥ predefined threshold(s) will be provided for each investigational product within each group at baseline and each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination The Clopper-Pearson method will be used to calculate the CIs. **Percentage of participants with the immune response (non-S) to SARS-CoV-2 for N-binding antibody at the time points when data are available** The Clopper-Pearson method will be used to calculate the CIs. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Endpoint	Statistical Analysis Methods
	RCDCs for immunogenicity results Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level after Dose 1 and after Dose 2.

9.4.2. Efficacy Analyses

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Endpoint	Statistical Analysis Methods
	The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.
Secondary	**First: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Second: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Third and fourth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Fifth and sixth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints will be evaluated descriptively with 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Endpoint	Statistical Analysis Methods
	Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days or from 14 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[9] Missing efficacy data will not be imputed.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Endpoint	Statistical Analysis Methods
	used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group. The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory	N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point,

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" and each lot of "Process 2" will be summarized descriptively. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected randomly for the analysis.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

centered at θ = 0.4118 (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 6 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8, for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall Type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

Only the first primary endpoint will be analyzed at IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints (confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and in all participants, confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection and in all participants) will be evaluated sequentially in the stated order, by the same method used for the evaluation of primary VE endpoints. Success thresholds for secondary VE endpoints will be appropriately chosen to control overall Type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeudrafting
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data (with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.
- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.
- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.
- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2.
- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.
- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Review of safety and/or immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review
- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.
- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Abbreviation	Term
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
non-S	nonspike protein
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Abbreviation	Term
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs after accrual of at least 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)
This document cannot be used to support and marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.

4 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

5 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

6 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

7 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

8 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

9 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

10 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 9, Clean Copy, 29Oct2020
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	30-Oct-2020 13:39:40	Business Line Approver
PPD	30-Oct-2020 13:40:22	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195653bd7\Approved\Approved On: 30-Oct-2020 13:40 (GMT)

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 8	15 October 2020	• Removed "N-binding antibody" and "SARS-CoV-2 detection by NAAT" as endpoints from the third exploratory objective, as these results are used for the determination of the population, and are not endpoints. • Clarified that the "Process 1" participants included in the descriptive analysis of "Process 1"- and "Process 2"-manufactured study interventions will be selected randomly. • Clarified that surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study. • Further modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Clarified that for participants who are not in the reactogenicity subset, local reactions and systemic events following vaccination should be detected and reported as AEs. • Clarified that premenarchal females are not WOCBP. • Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2. • Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2." • Clarified the degree of unblinding on the unblinded submissions team in Section 6.3.3. • Made provision for a second dose of BNT162b2 in participants who were affected by a medication error at Visit 2 in Section 6.6. • Provided further clarification regarding discontinuation of study intervention in Section 7.1.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Added that 2 periods of potential COVID-19 symptoms within 4 days will be considered as a single illness. • Provided guidance in Section 8.13 regarding circumstances in which a SARS-CoV-2 test might be required even if symptoms within 7 days following each vaccination are considered more likely due to vaccine reactogenicity. • Made allowance in Section 8.13 for a second SARS-CoV-2 test to be performed within the same potential COVID-19 illness if it is in accordance with routine practice. • Added Section 8.15 to describe the reporting of SARS-CoV-2 test results and their implications for participants receiving a second vaccine dose. • Added statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age. • Amended scope of analyses of safety data in Section 9.5.1. • Made various editorial changes.
Protocol amendment 6 (Germany-specific)	23 September 2020	• According to regulatory request, inclusion criterion 1 now specifies that participants less than 18 years of age will not be enrolled in the EU.
Protocol amendment 6	08 September 2020	• Reordered some procedures in the Phase 2/3 schedule of activities for consistency with the main body of the protocol. • Corrected the window for the 6-month follow-up visit to be approximately 6 months after Vaccination 2. • Reduced the volume of blood draws to ~20 mL. • Removed the need to have safety data reported for participants to be included in the safety objective assessment. • Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease. • Increased the sample size for Phase 2/3 to ~43,998. • Clarified that inclusion criterion 4 (ie, participants at higher risk for acquiring COVID-19) is applicable for Phase 2/3 only, and provided some examples.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Removed exclusion criterion 2 (ie, known infection with HIV, HCV, or HBV) for Phase 3 and added criteria for HIV-positive participants. • Decreased the lower age limit and removed the upper age limit for inclusion in Phase 2/3 in order to evaluate BNT162b2 30 µg in older adolescents and those over 85 years of age; updated the title and other references to adults to align with this change. • Renamed the immunological assays to align with other program-level documents. • Removed reference to the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) being "heads up." • Clarified that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention. • Added clarification that potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. • Updated the analysis population descriptions to align with the study SAP.
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7. • Updated the stopping and alert rule parameters for enhanced COVID-19.
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation, and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol. • To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions.

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial • Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 15
1. PROTOCOL SUMMARY 17
1.1. Synopsis 17
1.2. Schema 24
1.3. Schedule of Activities 25
1.3.1. Phase 1 25
1.3.2. Phase 2/3 30
2. INTRODUCTION 33
2.1. Study Rationale 33
2.2. Background 33
2.2.1. Clinical Overview 34
2.3. Benefit/Risk Assessment 34
2.3.1. Risk Assessment 36
2.3.2. Benefit Assessment 38
2.3.3. Overall Benefit/Risk Conclusion 38
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 38
3.1. For Phase 1 38
3.2. For Phase 2/3 40
4. STUDY DESIGN 42
4.1. Overall Design 42
4.1.1. Phase 1 43
4.1.2. Phase 2/3 44
4.2. Scientific Rationale for Study Design 45
4.3. Justification for Dose 45
4.4. End of Study Definition 46
5. STUDY POPULATION 47
5.1. Inclusion Criteria 47
5.2. Exclusion Criteria 48
5.3. Lifestyle Considerations 50
5.3.1. Contraception 50

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

5.4. Screen Failures 50
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 51
6. STUDY INTERVENTION 51
6.1. Study Intervention(s) Administered 52
6.1.1. Manufacturing Process 53
6.1.2. Administration 53
6.2. Preparation/Handling/Storage/Accountability 53
6.2.1. Preparation and Dispensing 54
6.3. Measures to Minimize Bias: Randomization and Blinding 55
6.3.1. Allocation to Study Intervention 55
6.3.2. Blinding of Site Personnel 55
6.3.3. Blinding of the Sponsor 55
6.3.4. Breaking the Blind 56
6.4. Study Intervention Compliance 56
6.5. Concomitant Therapy 57
6.5.1. Prohibited During the Study 57
6.5.2. Permitted During the Study 58
6.6. Dose Modification 58
6.7. Intervention After the End of the Study 59
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 59
7.1. Discontinuation of Study Intervention 59
7.2. Participant Discontinuation/Withdrawal From the Study 59
7.2.1. Withdrawal of Consent 60
7.3. Lost to Follow-up 60
8. STUDY ASSESSMENTS AND PROCEDURES 61
8.1. Efficacy and/or Immunogenicity Assessments 62
8.1.1. Biological Samples 64
8.2. Safety Assessments 65
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 65
8.2.2. Electronic Diary 66

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

8.2.2.1. Grading Scales 66
8.2.2.2. Local Reactions 66
8.2.2.3. Systemic Events 67
8.2.2.4. Fever 68
8.2.2.5. Antipyretic Medication 69
8.2.3. Phase 1 Stopping Rules 69
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 70
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 71
8.2.6. Pregnancy Testing 71
8.3. Adverse Events and Serious Adverse Events 72
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 72
8.3.1.1. Reporting SAEs to Pfizer Safety 73
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 73
8.3.2. Method of Detecting AEs and SAEs 73
8.3.3. Follow-up of AEs and SAEs 73
8.3.4. Regulatory Reporting Requirements for SAEs 74
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 74
8.3.5.1. Exposure During Pregnancy 74
8.3.5.2. Exposure During Breastfeeding 76
8.3.5.3. Occupational Exposure 76
8.3.6. Cardiovascular and Death Events 76
8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 77
8.3.8. Adverse Events of Special Interest 77
8.3.8.1. Lack of Efficacy 77
8.3.9. Medical Device Deficiencies 77
8.3.10. Medication Errors 77
8.4. Treatment of Overdose 78
8.5. Pharmacokinetics 79
8.6. Pharmacodynamics 79

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.7. Genetics 79
8.8. Biomarkers 79
8.9. Immunogenicity Assessments 79
8.10. Health Economics 79
8.11. Study Procedures 79
8.11.1. Phase 1 79
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 79
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 81
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 83
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 84
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 85
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 87
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 89
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 90
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4) 90
8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4) 91
8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4) 91
8.11.2. Phase 2/3 92
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 92
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 94
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2) 96
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2) 97
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2) 98

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2) 98
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 99
8.13. COVID-19 Surveillance (All Participants) 100
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 101
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit) 102
8.14. Communication and Use of Technology 103
8.15. SARS-CoV-2 NAAT Results From Visits 1 and 2 and Potential COVID-19 Illness Visits 104
9. STATISTICAL CONSIDERATIONS 104
9.1. Estimands and Statistical Hypotheses 105
9.1.1. Estimands 105
9.1.2. Statistical Hypotheses 105
9.1.2.1. Statistical Hypothesis Evaluation for Efficacy 105
9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity 105
9.2. Sample Size Determination 106
9.3. Analysis Sets 108
9.4. Statistical Analyses 108
9.4.1. Immunogenicity Analyses 109
9.4.2. Efficacy Analyses 114
9.4.3. Safety Analyses 115
9.4.4. Other Analyses 117
9.5. Interim Analyses 117
9.5.1. Analysis Timing 120
9.6. Data Monitoring Committee or Other Independent Oversight Committee 120
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 122
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 122
10.1.1. Regulatory and Ethical Considerations 122
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 122

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.1.2. Informed Consent Process 123
10.1.3. Data Protection 124
10.1.4. Dissemination of Clinical Study Data 124
10.1.5. Data Quality Assurance 125
10.1.6. Source Documents 127
10.1.7. Study and Site Start and Closure 127
10.1.8. Sponsor's Qualified Medical Personnel 128
10.2. Appendix 2: Clinical Laboratory Tests 129
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 131
10.3.1. Definition of AE 131
10.3.2. Definition of SAE 132
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 134
10.3.4. Reporting of SAEs 137
10.4. Appendix 4: Contraceptive Guidance 138
10.4.1. Male Participant Reproductive Inclusion Criteria 138
10.4.2. Female Participant Reproductive Inclusion Criteria 138
10.4.3. Woman of Childbearing Potential 139
10.4.4. Contraception Methods 140
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 142
10.6. Appendix 6: Abbreviations 144
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 148
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection 151
11. REFERENCES 152

LIST OF TABLES

Table 1. Local Reaction Grading Scale 67
Table 2. Systemic Event Grading Scale 68
Table 3. Scale for Fever 69
Table 4. Power Analysis for Noninferiority Assessment 107

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 107
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility 118
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses 119
Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall 119
Table 9. Laboratory Abnormality Grading Scale 129
Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 149
Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 150

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and efficacy of these prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the last dose • SAEs from Dose 1 to 7 days after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Objectives[a]	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in <u>all participants</u> randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100× (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Objectives[a]	Estimands	Endpoints
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• N-binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• All safety endpoints described above • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for a description of the manufacturing process.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

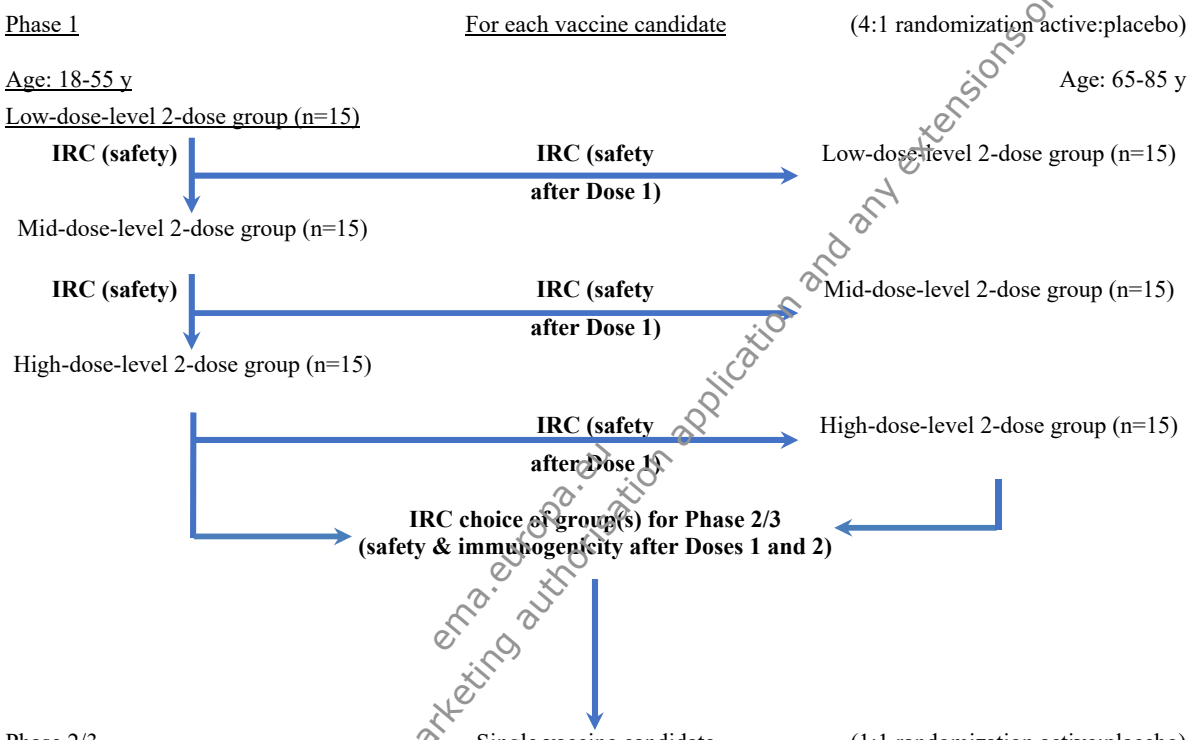
The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

Except for the objective to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age, the other immunogenicity

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, percentage of participants with ≥ specified threshold, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and/or RBD-binding IgG levels at the various time points.

1.2. Schema



Abbreviation: IRC = internal review committee.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

090177e19544379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						

This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[c]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19544379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~20 mL	~20 mL	~20 mL		~20 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X								
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X											
Provide thermometer and measuring device		X			X								
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►	◄	►							

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application											X		

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e19544379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C.

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X		
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL		~20 mL/ ~10 mL
Obtain nasal (midturbinate) swab	X	X					X	

090177e19544379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain randomization number and study intervention allocation	X							
Administer study intervention	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	←→	←→						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X	X[f]
Collect e-diary or assist the participant to delete application						X		

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e19544379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Two SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein-receptor binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding P2 S.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

the currently available therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.
- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.
- All participants 12 to 15 years of age will be included in the reactogenicity subset (see Section 8.2.2).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e19544379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e19544379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of a potentially efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the last dose • SAEs from Dose 1 to 7 days after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Objectives[a]	Estimands	Endpoints
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• N-binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• All safety endpoints described above • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for description of the manufacturing process.

This protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team,

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 250 participants from each of the 2 age groups (12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization. Note that participants <18 years of age cannot be enrolled in the EU.

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

Informed Consent:

5. Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu/
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - Chronic liver disease
    - Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
    - Resident in a long-term facility
    - BMI >30 kg/m^2
    - Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.au
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;
    - Sore throat;
    - Diarrhea;
    - Vomiting.
2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.
3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.
4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 2 investigational RNA vaccine candidates, with the addition of saline placebo, are the 3 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	10-, 20-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual subject assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).
- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.
- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants).

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, due to a medication error, a participant receives 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa), the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. In this situation:

- Obtain informed consent for administration of the additional dose.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

dose of BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s).

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms does not meet exclusion criterion 5 and should not result in discontinuation of study intervention, whereas a COVID-19 diagnosis does meet exclusion criterion 5 and should result in discontinuation of study intervention (see Section 8.15).

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

The total blood sampling volume for individual participants in this study is approximately up to: 515 mL for participants in Phase 1, 110 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum. Additionally, 20 mL of blood for participants ≥16 years of age and 10 mL for participants in the 12- to 15-year age stratum will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 700 mL during the 24-month study period. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
  - Fever;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction*;
  - Admission to an ICU;
  - Death.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu/
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

The DMC may recommend modification of the definition of severe disease according to emerging information.

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay
- S1-binding IgG level assay
- RBD-binding IgG level assay
- N-binding antibody assay

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2. For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with Section 8.3.2.

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be

This document can not be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the last dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccines SAE Report Form.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccines SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccines SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
  - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccines SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccines SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof are not covered

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccines SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccines SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccines SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

9. Contact the medical monitor within 24 hours.

10. Closely monitor the participant for any AEs/SAEs.

11. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

12. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Discuss contraceptive use as described in Section 10.4.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support a marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Fever ≥39.0°C (≥102.1°F).
- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

- Fever ≥39.0°C (≥102.1°F).
- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

- Fever ≥39.0°C (≥102.1°F).
- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.

This document cannot be used to support any marketing authorisation application ema.europa.eu and any extensions or variations thereof

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
    - Symptoms and signs, including

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

- Clinical diagnosis
- Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.
- Full blood count
- Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
- Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
- Number and type of any healthcare contact; duration of hospitalization and ICU stay
- Death

- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2 Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

8.15. SARS-CoV-2 NAAT Results From Visits 1 and 2 and Potential COVID-19 Illness Visits

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection.

- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result prior to Visit 2 should be handled as follows:

- Positive SARS-CoV-2 test with no symptoms, either at Visit 1 or any time between Visit 1 and Visit 2: A positive test in an asymptomatic participant does not meet exclusion criterion 5; therefore, Vaccination 2 should proceed as normal.

- Confirmed COVID-19 (ie, symptoms and positive SARS-CoV-2 test): This meets exclusion criterion 5; therefore, Vaccination 2 should not be given but the participant should remain in the study.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will be analyzed by all--available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either $VE_1 > 30\%$ or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

(Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2**.** If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

9.2. Sample Size Determination

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 250 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.623	-0.2	200	90.8%

Abbreviation: GMR = geometric mean ratio.

a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 1, N=12). Calculation may be updated if additional information becomes available to better estimate the standard deviation.

b. At 0.05 alpha level (2-sided).

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 vaccination. 2. All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application or any extensions or variations thereof

Endpoint	Statistical Analysis Methods
	assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Endpoint	Statistical Analysis Methods
	sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the 16- to 25-year age group)	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and 2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment. The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Endpoint	Statistical Analysis Methods
	be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with antibody levels ≥ predefined threshold(s) for SARS-CoV-2 serological parameters** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels and/or RBD-binding IgG levels, N-binding antibody, and SARS-CoV-2 detection by NAAT, percentages (and 2-sided 95% CIs) of participants with antibody levels ≥ predefined threshold(s) will be provided for each investigational product within each group at baseline and each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination The Clopper-Pearson method will be used to calculate the CIs. **Percentage of participants with the immune response (non-S) to SARS-CoV-2 for N-binding antibody at the time points when data are available**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Endpoint	Statistical Analysis Methods
	The Clopper-Pearson method will be used to calculate the CIs. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level after Dose 1 and after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

9.4.2. Efficacy Analyses

The statistical analysis of efficacy will be based on the evaluable efficacy population (primary analysis) and the all-available efficacy population as defined in Section 9.3.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in participants with and without evidence of infection before vaccination for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group after 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Endpoint	Statistical Analysis Methods
Secondary	**Ratio of confirmed severe COVID-19 illness per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** **Ratio of confirmed severe COVID-19 illness per 1000 person-years of follow-up for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints will be evaluated descriptively with 95% CIs. **Ratio of confirmed COVID-19 illness (according to the CDC-defined symptoms) per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** **Ratio of confirmed COVID-19 illness (according to the CDC-defined symptoms) per 1000 person-years of follow-up in participants with and without evidence of infection before vaccination for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms after 7 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[9] Missing efficacy data will not be imputed.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Endpoint	Statistical Analysis Methods
	For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after last dose will be provided for each vaccine group. The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
Pfizer Inc. Not for distribution

Endpoint	Statistical Analysis Methods
Exploratory	N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" and each lot of "Process 2" will be summarized descriptively. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected randomly for the analysis.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs are planned and will be performed by an unblinded statistical team after accrual of 32, 62, 92, and 120 cases. At each IA:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 6 illustrates the boundary for efficacy and futility if IAs are performed after accrual of 32 62, 92, and 120 cases in participants without evidence of infection before vaccination.

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
emea-xxxxxx
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.035	<0.001	0.003

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

After the primary objectives are met, the secondary VE endpoints (confirmed severe COVID-19 in participants without evidence of infection before vaccination and confirmed severe COVID-19 in all participants) will be evaluated sequentially, by the same method used for the primary VE endpoint evaluation. Success thresholds for secondary VE will be appropriately chosen to control overall Type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data (with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.
- IAs for efficacy at 32, 62, 92, and 120 cases and futility at 32, 62, and 92 cases.
- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2
- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2
- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.
- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Review of safety and/or immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review
- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. • Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccines SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccines SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccines SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccines SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccines SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccines SAE Report Form
• Facsimile transmission of the Vaccines SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccines SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccines SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.
- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorization application and any extensions or variations thereof

Abbreviation	Term
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
non-S	nonspike protein
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Abbreviation	Term
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs at 32, 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

This document cannot be used to support any marketing authorisation application and any extension of variations thereof
ema.europa.eu

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)
This document cannot be used to support and marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.

4 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

5 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

6 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

7 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

8 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

9 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

10 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 8, Clean Copy, 15Oct2020
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	15-Oct-2020 23:59:44	Final Approval
PPD	16-Oct-2020 06:36:29	Business Line Approver

090177e195444379\Approved\Approved On: 16-Oct-2020 06:36 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2. • Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2." • Clarified the degree of unblinding on the unblinded submissions team in Section 6.3.3. • Made provision for a second dose of BNT162b2 in participants who were affected by a medication error at Visit 2 in Section 6.6. • Provided further clarification regarding discontinuation of study intervention in Section 7.1. • Modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Added that 2 periods of potential COVID-19 symptoms within 4 days will be considered as a single illness. • Provided guidance in Section 8.13 regarding circumstances in which a SARS-CoV-2 test might be required even if symptoms within 7 days following each vaccination are considered more likely due to vaccine reactogenicity. • Made allowance in Section 8.13 for a second SARS-CoV-2 test to be performed within the same potential COVID-19 illness if it is in accordance with routine practice. • Added Section 8.15 to describe the reporting of SARS-CoV-2 test results and their implications for participants receiving a second vaccine dose. • Added statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Amended scope of analyses of safety data in Section 9.5.1. • Made various editorial changes.
Protocol amendment 6 (Germany-specific)	23 September 2020	• According to regulatory request, inclusion criterion 1 now specifies that participants less than 18 years of age will not be enrolled in the EU.
Protocol amendment 6	08 September 2020	• Reordered some procedures in the Phase 2/3 schedule of activities for consistency with the main body of the protocol. • Corrected the window for the 6-month follow-up visit to be approximately 6 months after Vaccination 2. • Reduced the volume of blood draws to ~20 mL. • Removed the need to have safety data reported for participants to be included in the safety objective assessment. • Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease. • Increased the sample size for Phase 2/3 to ~43,998. • Clarified that inclusion criterion 4 (ie, participants at higher risk for acquiring COVID-19) is applicable for Phase 2/3 only, and provided some examples. • Removed exclusion criterion 2 (ie, known infection with HIV, HCV, or HBV) for Phase 3 and added criteria for HIV-positive participants. • Decreased the lower age limit and removed the upper age limit for inclusion in Phase 2/3 in order to evaluate BNT162b2 30 µg in older adolescents and those over 85 years of age; updated the title and other references to adults to align with this change. • Renamed the immunological assays to align with other program-level documents. • Removed reference to the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) being “heads up.” • Clarified that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention. • Added clarification that potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. • Updated the analysis population descriptions to align with the study SAP.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory. • Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7. • Updated the stopping and alert rule parameters for enhanced COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 14
1. PROTOCOL SUMMARY 16
1.1. Synopsis 16
1.2. Schema 23
1.3. Schedule of Activities 24
1.3.1. Phase 1 24
1.3.2. Phase 2/3 29
2. INTRODUCTION 32
2.1. Study Rationale 32
2.2. Background 32
2.2.1. Clinical Overview 33
2.3. Benefit/Risk Assessment 33
2.3.1. Risk Assessment 35
2.3.2. Benefit Assessment 37
2.3.3. Overall Benefit/Risk Conclusion 37
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 37
3.1. For Phase 1 37
3.2. For Phase 2/3 39
4. STUDY DESIGN 41
4.1. Overall Design 41
4.1.1. Phase 1 42
4.1.2. Phase 2/3 43
4.2. Scientific Rationale for Study Design 44
4.3. Justification for Dose 44
4.4. End of Study Definition 45
5. STUDY POPULATION 46
5.1. Inclusion Criteria 46
5.2. Exclusion Criteria 47
5.3. Lifestyle Considerations 49
5.3.1. Contraception 49

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

5.4. Screen Failures 49
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 50
6. STUDY INTERVENTION 50
6.1. Study Intervention(s) Administered 51
6.1.1. Manufacturing Process 52
6.1.2. Administration 52
6.2. Preparation/Handling/Storage/Accountability 52
6.2.1. Preparation and Dispensing 53
6.3. Measures to Minimize Bias: Randomization and Blinding 54
6.3.1. Allocation to Study Intervention 54
6.3.2. Blinding of Site Personnel 54
6.3.3. Blinding of the Sponsor 54
6.3.4. Breaking the Blind 55
6.4. Study Intervention Compliance 55
6.5. Concomitant Therapy 56
6.5.1. Prohibited During the Study 56
6.5.2. Permitted During the Study 57
6.6. Dose Modification 57
6.7. Intervention After the End of the Study 58
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 58
7.1. Discontinuation of Study Intervention 58
7.2. Participant Discontinuation/Withdrawal From the Study 58
7.2.1. Withdrawal of Consent 59
7.3. Lost to Follow-up 59
8. STUDY ASSESSMENTS AND PROCEDURES 60
8.1. Efficacy and/or Immunogenicity Assessments 61
8.1.1. Biological Samples 63
8.2. Safety Assessments 64
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 64
8.2.2. Electronic Diary 65

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.2.2.1. Grading Scales 65
8.2.2.2. Local Reactions 65
8.2.2.3. Systemic Events 66
8.2.2.4. Fever 67
8.2.2.5. Antipyretic Medication 68
8.2.3. Phase 1 Stopping Rules 68
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 69
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 70
8.2.6. Pregnancy Testing 70
8.3. Adverse Events and Serious Adverse Events 71
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 71
8.3.1.1. Reporting SAEs to Pfizer Safety 72
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 72
8.3.2. Method of Detecting AEs and SAEs 72
8.3.3. Follow-up of AEs and SAEs 72
8.3.4. Regulatory Reporting Requirements for SAEs 73
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 73
8.3.5.1. Exposure During Pregnancy 73
8.3.5.2. Exposure During Breastfeeding 75
8.3.5.3. Occupational Exposure 75
8.3.6. Cardiovascular and Death Events 75
8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 76
8.3.8. Adverse Events of Special Interest 76
8.3.8.1. Lack of Efficacy 76
8.3.9. Medical Device Deficiencies 76
8.3.10. Medication Errors 76
8.4. Treatment of Overdose 77
8.5. Pharmacokinetics 78
8.6. Pharmacodynamics 78

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.7. Genetics 78
8.8. Biomarkers 78
8.9. Immunogenicity Assessments 78
8.10. Health Economics 78
8.11. Study Procedures 78
8.11.1. Phase 1 78
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 78
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 80
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 82
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 83
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 84
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 86
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 88
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 89
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4) 89
8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4) 90
8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4) 90
8.11.2. Phase 2/3 91
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 91
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 93
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2) 95
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2) 96
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2) 97

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2) 97
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 98
8.13. COVID-19 Surveillance (All Participants) 99
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 100
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit) 101
8.14. Communication and Use of Technology 102
8.15. SARS-CoV-2 NAAT Results From Visits 1 and 2 and Potential COVID-19 Illness Visits 103
9. STATISTICAL CONSIDERATIONS 103
9.1. Estimands and Statistical Hypotheses 103
9.1.1. Estimands 103
9.1.2. Statistical Hypotheses 104
9.1.2.1. Statistical Hypothesis Evaluation for Efficacy 104
9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity 104
9.2. Sample Size Determination 105
9.3. Analysis Sets 107
9.4. Statistical Analyses 107
9.4.1. Immunogenicity Analyses 108
9.4.2. Efficacy Analyses 113
9.4.3. Safety Analyses 114
9.4.4. Other Analyses 116
9.5. Interim Analyses 116
9.5.1. Analysis Timing 119
9.6. Data Monitoring Committee or Other Independent Oversight Committee 119
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 121
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 121
10.1.1. Regulatory and Ethical Considerations 121
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 121

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.1.2. Informed Consent Process 122
10.1.3. Data Protection 123
10.1.4. Dissemination of Clinical Study Data 123
10.1.5. Data Quality Assurance 124
10.1.6. Source Documents 126
10.1.7. Study and Site Start and Closure 126
10.1.8. Sponsor's Qualified Medical Personnel 127
10.2. Appendix 2: Clinical Laboratory Tests 128
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 130
10.3.1. Definition of AE 130
10.3.2. Definition of SAE 131
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 133
10.3.4. Reporting of SAEs 136
10.4. Appendix 4: Contraceptive Guidance 137
10.4.1. Male Participant Reproductive Inclusion Criteria 137
10.4.2. Female Participant Reproductive Inclusion Criteria 137
10.4.3. Woman of Childbearing Potential 138
10.4.4. Contraception Methods 139
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 141
10.6. Appendix 6: Abbreviations 143
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 147
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection 150
11. REFERENCES 151

LIST OF TABLES

Table 1. Local Reaction Grading Scale 66
Table 2. Systemic Event Grading Scale 67
Table 3. Scale for Fever 68
Table 4. Power Analysis for Noninferiority Assessment 106

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 106
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility 117
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses 118
Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall 118
Table 9. Laboratory Abnormality Grading Scale 128
Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 148
Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 149

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and efficacy of these prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
source: ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the last dose • SAEs from Dose 1 to 7 days after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Objectives[a]	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in <u>all participants</u> randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100× (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Objectives[a]	Estimands	Endpoints
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• N-binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers • N-binding antibody • SARS-CoV-2 detection by NAAT
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• All safety endpoints described above • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for a description of the manufacturing process.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

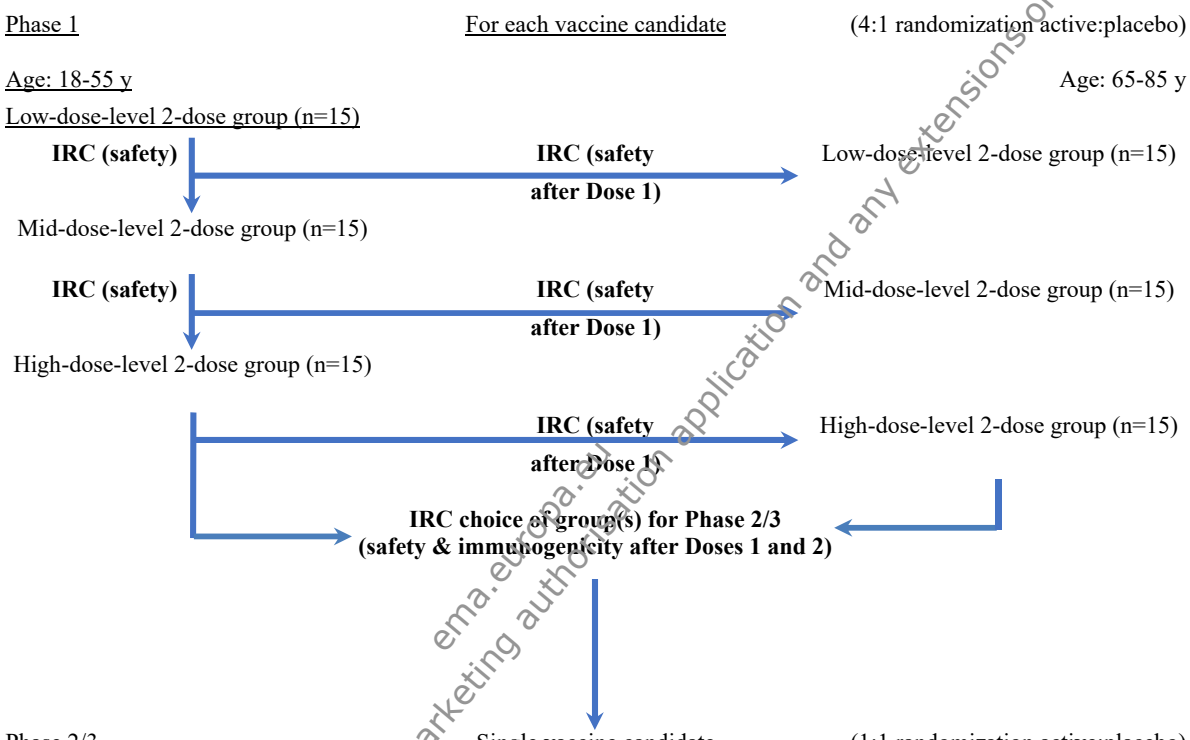
The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

Except for the objective to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age, the other immunogenicity

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, percentage of participants with ≥ specified threshold, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and/or RBD-binding IgG levels at the various time points.

1.2. Schema



Abbreviation: IRC = internal review committee.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						

This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[c]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~20 mL	~20 mL	~20 mL		~20 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X								
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X											
Provide thermometer and measuring device		X			X								
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►	◄	►							

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application											X		

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C.

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X		
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL		~20 mL/ ~10 mL
Obtain nasal (midturbinate) swab	X	X					X	

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain randomization number and study intervention allocation	X							
Administer study intervention	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	◄——►	◄——►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X	X[f]
Collect e-diary or assist the participant to delete application						X		

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Two SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2-mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein-receptor binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding P2 S.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

the currently available therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.
- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.
- All participants 12 to 15 years of age will be included in the reactogenicity subset (see Section 8.2.2).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of a potentially efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the last dose • SAEs from Dose 1 to 7 days after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Objectives[a]	Estimands	Endpoints
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• N-binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers • N-binding antibody • SARS-CoV-2 detection by NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Objectives[a]	Estimands	Endpoints
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• All safety endpoints described above • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for description of the manufacturing process.

This protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team,

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 250 participants from each of the 2 age groups (12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2," manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization. Note that participants <18 years of age cannot be enrolled in the EU.

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

Informed Consent:

5. Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - Chronic liver disease
    - Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
    - Resident in a long-term facility
    - BMI >30 kg/m^2
    - Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.au
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;
    - Sore throat;
    - Diarrhea;
    - Vomiting.
2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.
3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.
4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 2 investigational RNA vaccine candidates, with the addition of saline placebo, are the 3 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	10-, 20-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual subject assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).
- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.
- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants).

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, due to a medication error, a participant receives 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa), the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. In this situation:

- Obtain informed consent for administration of the additional dose.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

dose of BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s).

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms does not meet exclusion criterion 5 and should not result in discontinuation of study intervention, whereas a COVID-19 diagnosis does meet exclusion criterion 5 and should result in discontinuation of study intervention (see Section 8.15).

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

The total blood sampling volume for individual participants in this study is approximately up to: 515 mL for participants in Phase 1, 110 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum. Additionally, 20 mL of blood for participants ≥16 years of age and 10 mL for participants in the 12- to 15-year age stratum will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 700 mL during the 24-month study period. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if:

It was obtained using:

- An FDA-cleared assay; or an assay that is not FDA-cleared but was conducted in a laboratory that is currently CLIA-certified; or an assay performed by a laboratory accredited according to the ISO 15189 standard by a national or regional accreditation body;

AND

- The assay is deemed acceptable by Pfizer.

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- Significant acute renal, hepatic, or neurologic dysfunction*;
- Admission to an ICU;
- Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay
- S1-binding IgG level assay
- RBD-binding IgG level assay
- N-binding antibody assay

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2.

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the last dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccines SAE Report Form.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccines SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccines SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
  - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccines SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccines SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof are not covered

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccines SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccines SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccines SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Discuss contraceptive use as described in Section 10.4.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support a marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- Fever ≥39.0°C (≥102.1°F).
- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

- Fever ≥39.0°C (≥102.1°F).
- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

- Fever ≥39.0°C (≥102.1°F).
- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application. ema.europa.eu/ema/ any extensions or variations thereof

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support my marketing authorisation application and any extensions or variations thereof

- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
    - Symptoms and signs, including
        - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
        - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- Significant acute renal, hepatic, or neurologic dysfunction
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

- Clinical diagnosis
- Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.
- Full blood count
- Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
- Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
- Number and type of any healthcare contact; duration of hospitalization and ICU stay
- Death

- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

This document is released to support any marketing authorisation application and any extensions or variations thereof
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

8.15. SARS-CoV-2 NAAT Results From Visits 1 and 2 and Potential COVID-19 Illness Visits

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection.

- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result prior to Visit 2 should be handled as follows:

- Positive SARS-CoV-2 test with no symptoms, either at Visit 1 or any time between Visit 1 and Visit 2: A positive test in an asymptomatic participant does not meet exclusion criterion 5; therefore, Vaccination 2 should proceed as normal.

- Confirmed COVID-19 (ie, symptoms and positive SARS-CoV-2 test): This meets exclusion criterion 5; therefore, Vaccination 2 should not be given but the participant should remain in the study.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will be analyzed by all--available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either $VE_1 > 30\%$ or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2**.** If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

9.2. Sample Size Determination

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 250 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

This document cannot be used to support initial marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.623	-0.2	200	90.8%

Abbreviation: GMR = geometric mean ratio.

a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 1, N=12). Calculation may be updated if additional information becomes available to better estimate the standard deviation.

b. At 0.05 alpha level (2-sided).

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 vaccination. 2. All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application or any extensions or variations thereof

Endpoint	Statistical Analysis Methods
	assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in

This document cannot be used to support any marketing authorisation application on ema.europa.eu and any extensions or variations thereof

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Endpoint	Statistical Analysis Methods
	sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the 16- to 25-year age group)	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and 2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment. The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Endpoint	Statistical Analysis Methods
	be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with antibody levels ≥ predefined threshold(s) for SARS-CoV-2 serological parameters** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels and/or RBD-binding IgG levels, N-binding antibody, and SARS-CoV-2 detection by NAAT, percentages (and 2-sided 95% CIs) of participants with antibody levels ≥ predefined threshold(s) will be provided for each investigational product within each group at baseline and each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination The Clopper-Pearson method will be used to calculate the CIs. **Percentage of participants with the immune response (non-S) to SARS-CoV-2 for N-binding antibody at the time points when data are available**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Endpoint	Statistical Analysis Methods
	The Clopper-Pearson method will be used to calculate the CIs. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level after Dose 1 and after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

9.4.2. Efficacy Analyses

The statistical analysis of efficacy will be based on the evaluable efficacy population (primary analysis) and the all-available efficacy population as defined in Section 9.3.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in participants with and without evidence of infection before vaccination for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group after 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Endpoint	Statistical Analysis Methods
Secondary	**Ratio of confirmed severe COVID-19 illness per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** **Ratio of confirmed severe COVID-19 illness per 1000 person-years of follow-up for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints will be evaluated descriptively with 95% CIs. **Ratio of confirmed COVID-19 illness (according to the CDC-defined symptoms) per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** **Ratio of confirmed COVID-19 illness (according to the CDC-defined symptoms) per 1000 person-years of follow-up in participants with and without evidence of infection before vaccination for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms after 7 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[9] Missing efficacy data will not be imputed.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Endpoint	Statistical Analysis Methods
	For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after last dose will be provided for each vaccine group. The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Endpoint	Statistical Analysis Methods
Exploratory	N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2" will be summarized descriptively.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs are planned and will be performed by an unblinded statistical team after accrual of 32, 62, 92, and 120 cases. At each IA:

- VE for the first primary objective will be evaluated . Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 6 illustrates the boundary for efficacy and futility if IAs are performed after accrual of 32 62, 92, and 120 cases in participants without evidence of infection before vaccination.

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
Pfizer exhibit

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

After the primary objectives are met, the secondary VE endpoints (confirmed severe COVID-19 in participants without evidence of infection before vaccination and confirmed severe COVID-19 in all participants) will be evaluated sequentially, by the same method used for the primary VE endpoint evaluation. Success thresholds for secondary VE will be appropriately chosen to control overall Type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data (with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.
- IAs for efficacy at 32, 62, 92, and 120 cases and futility at 32, 62, and 92 cases.
- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2
- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2
- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.
- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Review of safety and/or immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review
- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccines SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccines SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccines SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccines SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccines SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccines SAE Report Form
• Facsimile transmission of the Vaccines SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccines SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccines SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.
- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
non-S	nonspike protein
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Abbreviation	Term
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs at 32, 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)
This document cannot be used to support and marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.

4 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

5 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

6 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

7 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

8 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

9 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

10 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 7, Clean Copy, 06Oct2020
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	07-Oct-2020 02:48:54	Final Approval
PPD	07-Oct-2020 08:40:24	Business Line Approver

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1951cd87d\Approved\Approved On: 07-Oct-2020 08:40 (GMT)

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 6	08 September 2020	• Reordered some procedures in the Phase 2/3 schedule of activities for consistency with the main body of the protocol. • Corrected the window for the 6-month follow-up visit to be approximately 6 months after Vaccination 2. • Reduced the volume of blood draws to ~20 mL. • Removed the need to have safety data reported for participants to be included in the safety objective assessment. • Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease. • Increased the sample size for Phase 2/3 to ~43,998. • Clarified that inclusion criterion 4 (ie, participants at higher risk for acquiring COVID-19) is applicable for Phase 2/3 only, and provided some examples. • Removed exclusion criterion 2 (ie, known infection with HIV, HCV, or HBV) for Phase 3 and added criteria for HIV-positive participants. • Decreased the lower age limit and removed the upper age limit for inclusion in Phase 2/3 in order to evaluate BNT162b2 30 µg in older adolescents and those over 85 years of age; updated the title and other references to adults to align with this change. • Renamed the immunological assays to align with other program-level documents. • Removed reference to the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) being "heads up." • Clarified that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention. • Added clarification that potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. • Updated the analysis population descriptions to align with the study SAP.
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory. • Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7. • Updated the stopping and alert rule parameters for enhanced COVID-19.
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation, and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol. • To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial • Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 13
1. PROTOCOL SUMMARY 15
1.1. Synopsis 15
1.2. Schema 22
1.3. Schedule of Activities 23
1.3.1. Phase 1 23
1.3.2. Phase 2/3 28
2. INTRODUCTION 30
2.1. Study Rationale 30
2.2. Background 30
2.2.1. Clinical Overview 31
2.3. Benefit/Risk Assessment 31
2.3.1. Risk Assessment 33
2.3.2. Benefit Assessment 34
2.3.3. Overall Benefit/Risk Conclusion 34
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 34
3.1. For Phase 1 34
3.2. For Phase 2/3 36
4. STUDY DESIGN 38
4.1. Overall Design 38
4.1.1. Phase 1 39
4.1.2. Phase 2/3 40
4.2. Scientific Rationale for Study Design 40
4.3. Justification for Dose 41
4.4. End of Study Definition 42
5. STUDY POPULATION 42
5.1. Inclusion Criteria 42
5.2. Exclusion Criteria 43
5.3. Lifestyle Considerations 45
5.3.1. Contraception 45

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

5.4. Screen Failures 46
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 46
6. STUDY INTERVENTION 47
6.1. Study Intervention(s) Administered 47
6.1.1. Administration 48
6.2. Preparation/Handling/Storage/Accountability 48
6.2.1. Preparation and Dispensing 49
6.3. Measures to Minimize Bias: Randomization and Blinding 50
6.3.1. Allocation to Study Intervention 50
6.3.2. Blinding of Site Personnel 50
6.3.3. Blinding of the Sponsor 50
6.3.4. Breaking the Blind 51
6.4. Study Intervention Compliance 51
6.5. Concomitant Therapy 51
6.5.1. Prohibited During the Study 52
6.5.2. Permitted During the Study 52
6.6. Dose Modification 53
6.7. Intervention After the End of the Study 53
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 53
7.1. Discontinuation of Study Intervention 53
7.2. Participant Discontinuation/Withdrawal From the Study 53
7.2.1. Withdrawal of Consent 54
7.3. Lost to Follow-up 54
8. STUDY ASSESSMENTS AND PROCEDURES 55
8.1. Efficacy and/or Immunogenicity Assessments 56
8.1.1. Biological Samples 58
8.2. Safety Assessments 59
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 59
8.2.2. Electronic Diary 60
8.2.2.1. Grading Scales 60

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

8.2.2.2. Local Reactions 60
8.2.2.3. Systemic Events 61
8.2.2.4. Fever 62
8.2.2.5. Antipyretic Medication 63
8.2.3. Phase 1 Stopping Rules 63
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 64
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 65
8.2.6. Pregnancy Testing 65
8.3. Adverse Events and Serious Adverse Events 66
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 66
8.3.1.1. Reporting SAEs to Pfizer Safety 67
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 67
8.3.2. Method of Detecting AEs and SAEs 67
8.3.3. Follow-up of AEs and SAEs 67
8.3.4. Regulatory Reporting Requirements for SAEs 68
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 68
8.3.5.1. Exposure During Pregnancy 68
8.3.5.2. Exposure During Breastfeeding 70
8.3.5.3. Occupational Exposure 70
8.3.6. Cardiovascular and Death Events 70
8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 71
8.3.8. Adverse Events of Special Interest 71
8.3.8.1. Lack of Efficacy 71
8.3.9. Medical Device Deficiencies 71
8.3.10. Medication Errors 71
8.4. Treatment of Overdose 72
8.5. Pharmacokinetics 73
8.6. Pharmacodynamics 73
8.7. Genetics 73

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu

8.8. Biomarkers 73
8.9. Immunogenicity Assessments 73
8.10. Health Economics 73
8.11. Study Procedures 73
8.11.1. Phase 1 73
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 73
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 74
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 77
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 78
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 79
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 81
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 82
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 83
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4) 84
8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4) 85
8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4) 85
8.11.2. Phase 2/3 86
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 86
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 88
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2) 90
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2) 91
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2) 91
8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2) 92

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 92
8.13. COVID-19 Surveillance (All Participants) 94
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 94
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit) 96
8.14. Communication and Use of Technology 97
9. STATISTICAL CONSIDERATIONS 97
9.1. Estimands and Statistical Hypotheses 97
9.1.1. Estimands 97
9.1.2. Statistical Hypotheses 98
9.2. Sample Size Determination 98
9.3. Analysis Sets 99
9.4. Statistical Analyses 100
9.4.1. Immunogenicity Analyses 100
9.4.2. Efficacy Analyses 105
9.4.3. Safety Analyses 106
9.4.4. Other Analyses 108
9.5. Interim Analyses 108
9.5.1. Analysis Timing 111
9.6. Data Monitoring Committee or Other Independent Oversight Committee 111
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 113
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 113
10.1.1. Regulatory and Ethical Considerations 113
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 113
10.1.2. Informed Consent Process 114
10.1.3. Data Protection 115
10.1.4. Dissemination of Clinical Study Data 115
10.1.5. Data Quality Assurance 116
10.1.6. Source Documents 118
10.1.7. Study and Site Start and Closure 118

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

10.1.8. Sponsor's Qualified Medical Personnel 119
10.2. Appendix 2: Clinical Laboratory Tests 120
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 122
10.3.1. Definition of AE 122
10.3.2. Definition of SAE 123
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 125
10.3.4. Reporting of SAEs 128
10.4. Appendix 4: Contraceptive Guidance 129
10.4.1. Male Participant Reproductive Inclusion Criteria 129
10.4.2. Female Participant Reproductive Inclusion Criteria 129
10.4.3. Woman of Childbearing Potential 130
10.4.4. Contraception Methods 131
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 133
10.6. Appendix 6: Abbreviations 135
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 139
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection 142
11. REFERENCES 143

LIST OF TABLES

Table 1. Local Reaction Grading Scale 61
Table 2. Systemic Event Grading Scale 62
Table 3. Scale for Fever 63
Table 4. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 99
Table 5. Interim Analysis Plan and Boundaries for Efficacy and Futility 109
Table 6. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses 110
Table 7. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall 110
Table 8. Laboratory Abnormality Grading Scale 120

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Table 9. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 140

Table 10. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 141

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and efficacy of these prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Objectives[a]	Estimands	Endpoints
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the last dose • SAEs from Dose 1 to 7 days after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Objectives[a]	Estimands	Endpoints
Exploratory		
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• N-binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers N-binding antibody • SARS-CoV-2 detection by NAAT
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥16 years of age [stratified as ≤55 or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥16 years of age [stratified as ≤55 or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

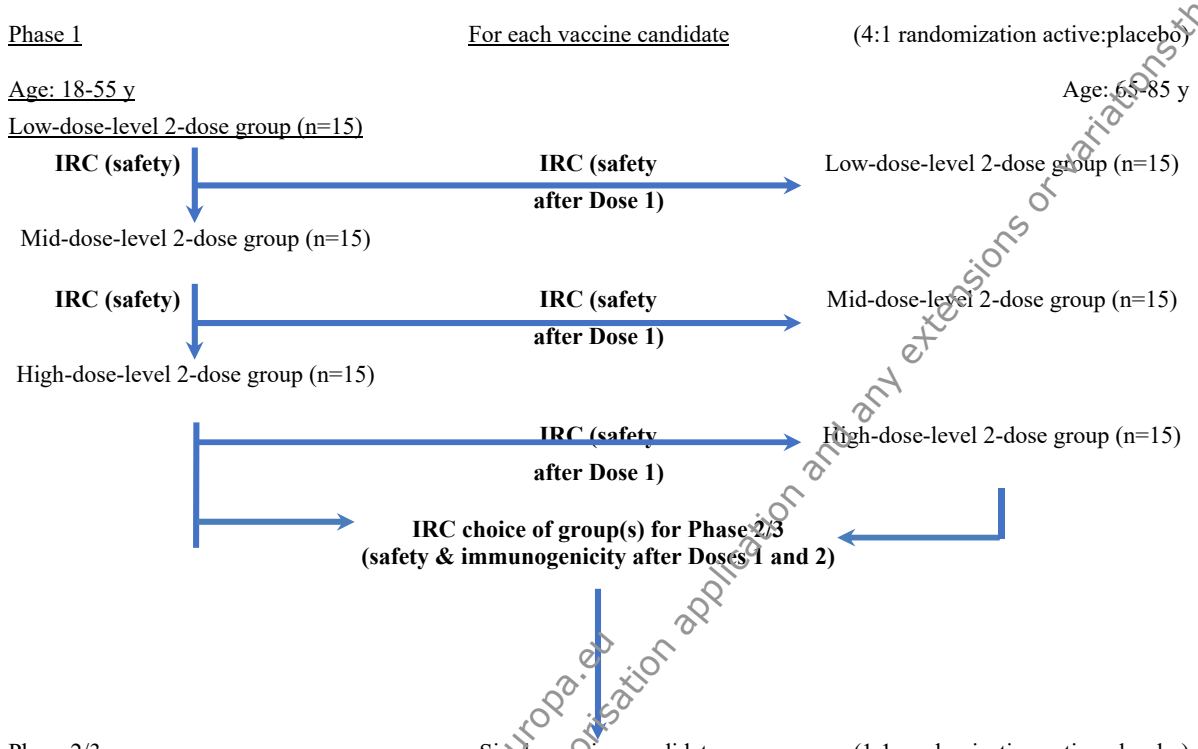
VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

The immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, percentage of participants with ≥ specified threshold, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels at the various time points.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

1.2. Schema



Abbreviation: IRC = internal review committee.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						

This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[c]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~20 mL	~20 mL	~20 mL		~20 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X								
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X											
Provide thermometer and measuring device		X			X								
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄———		———►	◄———	———►							

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application											X		

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	1	2	3	4	5	6	Unplanned 2	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
For participants who are HIV positive, record latest CD4 count and HIV viral load	X		X	X	X	X		
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment[d]	~20 mL		~20 mL	~20 mL	~20 mL	~20 mL		~20 mL
Obtain nasal (midturbinate) swab	X	X					X	
Obtain randomization number and study intervention allocation	X							

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Administer study intervention	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[d]	◄——►	◄——►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[d]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X[e]	X[e]	X[e]	X	X[e]
Collect e-diary or assist the participant to delete application						X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. Reactogenicity subset participants only.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu/
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Two SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2-mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein-receptor binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding P2 S.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with the currently available

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with possible current clinical COVID-19. All participants are followed for SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers, and COVID-19 illness, including markers of severity.
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of a potentially efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic and antibody testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the last dose • SAEs from Dose 1 to 7 days after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• AEs • SAEs • In a subset of at least 6000 participants: ○ Local reactions (pain at the injection site, redness, and swelling) ○ Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emea.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Exploratory		
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• N-binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers • N-binding antibody • SARS-CoV-2 detection by NAAT
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.

This protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥16 years of age [stratified as ≤55 or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥16 years of age, stratified as follows: 16 to 55 years or >55 years. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the last dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the last dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥16 years (Phase 2/3), at randomization.

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

Informed Consent:

5. Capable of giving personal signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. Previous clinical or microbiological diagnosis of COVID-19.

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - Chronic liver disease

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
- Resident in a long-term facility
- BMI >30 kg/m^2
- Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;
    - Sore throat;
    - Diarrhea;
    - Vomiting.
2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.
3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥16 years of age [stratified as ≤55 or >55 years of age]).

These 2 investigational RNA vaccine candidates, with the addition of saline placebo, are the 3 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	10-, 20-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
	required per country requirement	required per country requirement	labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. All statistical analyses conducted on Phase 2/3 data while the study is ongoing, that are not in support of the DMC, will be performed by this team. This team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants).

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). Note that a positive SARS-CoV-2 NAAT result without symptoms should not result in discontinuation of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcomes if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately up to 515 mL for participants in Phase 1, and approximately up to 110 mL for Phase 2/3 participants. Additionally, 20 mL of blood will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 700 mL during the 24-month study period. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. A local NAAT result will be considered acceptable if it was obtained using:

- An FDA-cleared (including Emergency Use Authorization) assay; or
- An assay that is not FDA-cleared but was conducted in a laboratory that is currently CLIA-certified; or
- An assay performed by a laboratory accredited according to the ISO 15189 standard by a national or regional accreditation body.

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction*;
  - Admission to an ICU;

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay
- S1-binding IgG level assay
- RBD-binding IgG level assay
- N-binding antibody assay

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2.

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV positive will be included in this subset. The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the last dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.au
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccines SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccines SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccines SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccines SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccines SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccines SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccines SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccines SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof are not the european patent office

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 100 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary if he/she is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- If the participant is part of the reactogenicity subset, ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).

- Measure the participant's body temperature.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Obtain a nasal (midturbinate) swab (collected by site staff).

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- If the participant is part of the reactogenicity subset, ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- The participant recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory. The result from this swab will be provided to the site once it is available, but this will not be in real time, and cannot be relied upon to direct clinical care. Therefore, the participant should be encouraged to seek care, if appropriate, from his or her usual provider.

- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:

  - Symptoms and signs, including

    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)

    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)

    - Significant acute renal, hepatic, or neurologic dysfunction

    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

  - Clinical diagnosis

  - Local laboratory COVID-19 test result

  - Full blood count

  - Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein

  - Imaging results (eg, CT or MRI scan) to document neurologic dysfunction

  - Number and type of any healthcare contact; duration of hospitalization and ICU stay

  - Death

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any variations or variations thereof
ema.europa.eu

- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant and the study site staff will be established. The participant may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant to report whether or not he or she has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant to ascertain why and also to obtain details of any missed events.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will be analyzed by all--available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either $VE_1 > 30\%$ or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

9.2. Sample Size Determination

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

For Phase 2/3, with assumptions of a true VE of 60% after the last dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

For safety outcomes, Table 4 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 4. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Population	Description
	first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other major protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other major protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other major protocol deviations as determined by the clinician.
All-available efficacy	1. All eligible randomized participants who receive at least 1 vaccination. 2. All eligible randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Endpoint	Statistical Analysis Methods
	Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Endpoint	Statistical Analysis Methods
Exploratory immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with antibody levels ≥ predefined threshold(s) for SARS-CoV-2 serological parameters**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Endpoint	Statistical Analysis Methods
	For SARS-CoV-2 neutralizing titers, S1-binding IgG levels and/or RBD-binding IgG levels, N-binding antibody, and SARS-CoV-2 detection by NAAT, percentages (and 2-sided 95% CIs) of participants with antibody levels ≥ predefined threshold(s) will be provided for each investigational product within each group at baseline and each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination The Clopper-Pearson method will be used to calculate the CIs. **Percentage of participants with the immune response (non-S) to SARS-CoV-2 for N-binding antibody at the time points when data are available** The Clopper-Pearson method will be used to calculate the CIs. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level after Dose 1 and after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

9.4.2. Efficacy Analyses

The statistical analysis of efficacy will be based on the evaluable efficacy population (primary analysis) and the all-available efficacy population as defined in Section 9.3.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group 7 days after the last dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in participants with and without evidence of infection before vaccination for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group after 7 days after the last dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Endpoint	Statistical Analysis Methods
Secondary	**Ratio of confirmed severe COVID-19 illness per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** **Ratio of confirmed severe COVID-19 illness per 1000 person-years of follow-up for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints will be evaluated descriptively with 95% CIs. **Ratio of confirmed COVID-19 illness (according to the CDC-defined symptoms) per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** **Ratio of confirmed COVID-19 illness (according to the CDC-defined symptoms) per 1000 person-years of follow-up in participants with and without evidence of infection before vaccination for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms after 7 days after the last dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[9] Missing efficacy data will not be imputed.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Endpoint	Statistical Analysis Methods
	For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after last dose will be provided for each vaccine group. The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Endpoint	Statistical Analysis Methods
Exploratory	N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs are planned and will be performed by an unblinded statistical team after accrual of 32, 62, 92, and 120 cases. At each IA:

- VE for the first primary objective will be evaluated . Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

informative beta prior, beta (0.700102, 1), is proposed for θ = (1-VE)/(2-VE). The prior is centered at θ = 0.4118 (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 5 illustrates the boundary for efficacy and futility if IAs are performed after accrual of 32 62, 92, and 120 cases in participants without evidence of infection before vaccination.

Table 5. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 6 and Table 7.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Table 6. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.035	<0.001	0.003

Table 7. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the last dose of investigational product onwards.

After the primary objectives are met, the secondary VE endpoints (confirmed severe COVID-19 in participants without evidence of infection before vaccination and confirmed severe COVID-19 in all participants) will be evaluated sequentially, by the same method used for the primary VE endpoint evaluation. Success thresholds for secondary VE will be appropriately chosen to control overall Type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

This document can only be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from the first 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3.
- IAs for efficacy at 32, 62, 92, and 120 cases and futility at 32, 62, and 92 cases.
- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.
- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met
- Review of safety and/or immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 8).

Table 8. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Table 8. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. • Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccines SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccines SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccines SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccines SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccines SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccines SAE Report Form
• Facsimile transmission of the Vaccines SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccines SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccines SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use application
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
non-S	nonspike protein
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal
uRNA	unmodified messenger ribonucleic acid

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Abbreviation	Term
US	United States
vax	vaccination
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs at 32, 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 9 and Table 10, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

This document cannot be used to support any marketing authorisation application and any extension of variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Table 9. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 10. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)
This document cannot be used to support and marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ⩾12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ⩾6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.

4 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

5 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

6 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

7 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

8 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

9 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

10 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 6, Clean Copy, 08 Sep 2020
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	08-Sep-2020 21:21:37	Business Line Approver
PPD	08-Sep-2020 23:40:23	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e194dca764\Approved\Approved On: 08-Sep-2020 23:40 (GMT)

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY ADULTS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory. • Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Updated the stopping and alert rule parameters for enhanced COVID-19.
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation, and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		candidates have been removed from the protocol. • To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		age cohort and advancement to groups of participants 65 to 85 years of age In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial • Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 12
1. PROTOCOL SUMMARY 14
1.1. Synopsis 14
1.2. Schema 21
1.3. Schedule of Activities 22
1.3.1. Phase 1 22
1.3.2. Phase 2/3 27
2. INTRODUCTION 29
2.1. Study Rationale 29
2.2. Background 29
2.2.1. Clinical Overview 30
2.3. Benefit/Risk Assessment 30
2.3.1. Risk Assessment 31
2.3.2. Benefit Assessment 32
2.3.3. Overall Benefit/Risk Conclusion 32
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 32
3.1. For Phase 1 32
3.2. For Phase 2/3 34
4. STUDY DESIGN 36
4.1. Overall Design 36
4.1.1. Phase 1 36
4.1.2. Phase 2/3 37
4.2. Scientific Rationale for Study Design 38
4.3. Justification for Dose 38
4.4. End of Study Definition 39
5. STUDY POPULATION 40
5.1. Inclusion Criteria 40
5.2. Exclusion Criteria 41
5.3. Lifestyle Considerations 43
5.3.1. Contraception 43

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

5.4. Screen Failures 43
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 44
6. STUDY INTERVENTION 44
6.1. Study Intervention(s) Administered 45
6.1.1. Administration 45
6.2. Preparation/Handling/Storage/Accountability 46
6.2.1. Preparation and Dispensing 47
6.3. Measures to Minimize Bias: Randomization and Blinding 47
6.3.1. Allocation to Study Intervention 47
6.3.2. Blinding of Site Personnel 48
6.3.3. Blinding of the Sponsor 48
6.3.4. Breaking the Blind 49
6.4. Study Intervention Compliance 49
6.5. Concomitant Therapy 49
6.5.1. Prohibited During the Study 49
6.5.2. Permitted During the Study 50
6.6. Dose Modification 50
6.7. Intervention After the End of the Study 50
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 51
7.1. Discontinuation of Study Intervention 51
7.2. Participant Discontinuation/Withdrawal From the Study 51
7.2.1. Withdrawal of Consent 52
7.3. Lost to Follow-up 52
8. STUDY ASSESSMENTS AND PROCEDURES 53
8.1. Efficacy and/or Immunogenicity Assessments 54
8.1.1. Biological Samples 56
8.2. Safety Assessments 57
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only) 57
8.2.2. Electronic Diary 58
8.2.2.1. Grading Scales 58

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.2.2.2. Local Reactions 58
8.2.2.3. Systemic Events 59
8.2.2.4. Fever 60
8.2.2.5. Antipyretic Medication 61
8.2.3. Phase 1 Stopping Rules 61
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 62
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 63
8.2.6. Pregnancy Testing 63
8.3. Adverse Events and Serious Adverse Events 64
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 64
8.3.1.1. Reporting SAEs to Pfizer Safety 65
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 65
8.3.2. Method of Detecting AEs and SAEs 65
8.3.3. Follow-up of AEs and SAEs 65
8.3.4. Regulatory Reporting Requirements for SAEs 66
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 66
8.3.5.1. Exposure During Pregnancy 66
8.3.5.2. Exposure During Breastfeeding 68
8.3.5.3. Occupational Exposure 68
8.3.6. Cardiovascular and Death Events 68
8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 69
8.3.8. Adverse Events of Special Interest 69
8.3.8.1. Lack of Efficacy 69
8.3.9. Medical Device Deficiencies 69
8.3.10. Medication Errors 69
8.4. Treatment of Overdose 70
8.5. Pharmacokinetics 71
8.6. Pharmacodynamics 71
8.7. Genetics 71

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.8. Biomarkers 71
8.9. Immunogenicity Assessments 71
8.10. Health Economics 71
8.11. Study Procedures 71
8.11.1. Phase 1 71
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 71
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 72
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 75
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 76
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 77
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 79
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 80
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 81
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 4) 82
8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4) 83
8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4) 83
8.11.2. Phase 2/3 84
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 84
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 86
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2) 88
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 2) 89
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2) 89
8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2) 90

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 90
8.13. COVID-19 Surveillance (All Participants) 91
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 92
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit) 93
8.14. Communication and Use of Technology 94
9. STATISTICAL CONSIDERATIONS 94
9.1. Estimands and Statistical Hypotheses 94
9.1.1. Estimands 94
9.1.2. Statistical Hypotheses 95
9.2. Sample Size Determination 95
9.3. Analysis Sets 96
9.4. Statistical Analyses 97
9.4.1. Immunogenicity Analyses 98
9.4.2. Efficacy Analyses 102
9.4.3. Safety Analyses 104
9.4.4. Other Analyses 105
9.5. Interim Analyses 105
9.5.1. Analysis Timing 108
9.6. Data Monitoring Committee or Other Independent Oversight Committee 108
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 110
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 110
10.1.1. Regulatory and Ethical Considerations 110
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 110
10.1.2. Informed Consent Process 111
10.1.3. Data Protection 112
10.1.4. Dissemination of Clinical Study Data 112
10.1.5. Data Quality Assurance 113
10.1.6. Source Documents 115
10.1.7. Study and Site Start and Closure 115

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

10.1.8. Sponsor's Qualified Medical Personnel 116
10.2. Appendix 2: Clinical Laboratory Tests 117
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 119
10.3.1. Definition of AE 119
10.3.2. Definition of SAE 120
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 122
10.3.4. Reporting of SAEs 125
10.4. Appendix 4: Contraceptive Guidance 126
10.4.1. Male Participant Reproductive Inclusion Criteria 126
10.4.2. Female Participant Reproductive Inclusion Criteria 126
10.4.3. Woman of Childbearing Potential 127
10.4.4. Contraception Methods 128
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 130
10.6. Appendix 6: Abbreviations 132
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 136
11. REFERENCES 139

LIST OF TABLES

Table 1. Local Reaction Grading Scale 59
Table 2. Systemic Event Grading Scale 60
Table 3. Scale for Fever 61
Table 4. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 96
Table 5. Interim Analysis Plan and Boundaries for Efficacy and Futility 106
Table 6. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses 107
Table 7. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall 107
Table 8. Laboratory Abnormality Grading Scale 117
Table 9. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 137

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 10. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 138

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and efficacy of these prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 serum neutralizing titers

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 serum neutralizing titers to the geometric mean of SARS-CoV-2–binding antibody levels at each time point	• SARS-CoV-2 serum neutralizing titers • SARS-CoV-2 anti-S1 binding antibody levels • SARS-CoV-2 anti-RBD binding antibody levels

For Phase 2/3

Objectives	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Objectives	Estimands	Endpoints
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emanuele.pera@ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Objectives	Estimands	Endpoints
Exploratory		
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	• SARS-CoV-2 anti-S1 binding antibody levels and/or anti-RBD binding antibody levels • SARS-CoV-2 serum neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• SARS-CoV-2 NVA-specific binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• SARS-CoV-2 anti-S1 binding antibody levels and/or anti-RBD binding antibody levels • SARS-CoV-2 serum neutralizing titers • SARS-CoV-2 NVA-specific binding antibody • SARS-CoV-2 detection by NAAT

Overall Design

This is a Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy adults.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: 18 to 85 years of age [stratified as ≤55 or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 14,643 vaccine recipients. It is intended that a minimum of 40% of participants will be in the 56- to 85-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: 18 to 85 years of age [stratified as ≤55 or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 29,286 participants

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

(14,643 vaccine recipients), based on the assumption of a 1.0% per year incidence in the placebo group, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

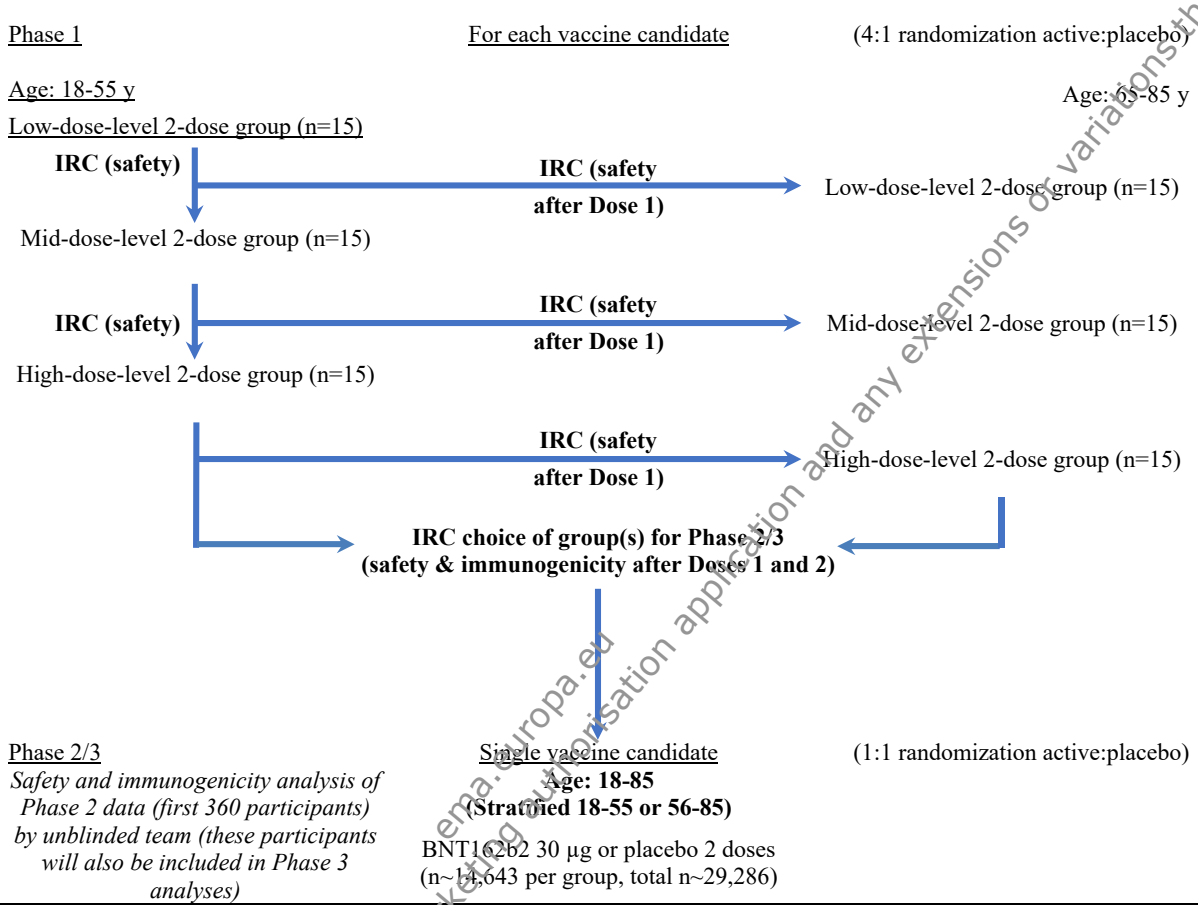
VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

The immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 serum neutralizing titers, SARS-CoV-2 anti-S1 binding antibody levels, and anti-RBD binding antibody levels at the various time points.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

1.2. Schema



Abbreviation: IRC = internal review committee.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						

This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[c]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL	~50 mL	~50 mL		~50 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X								
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X											
Provide thermometer and measuring device		X			X								
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►	◄	►							

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application											X		

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	1	2	3	4	5	6	Unplanned 3	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
Measure height and weight	X							
Perform urine pregnancy test (if appropriate)	X	X						
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Measure temperature (body)	X	X						
Review temporary delay criteria	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect blood sample for immunogenicity assessment	~25 mL		~25 mL	~25 mL	~25 mL	~25 mL		~50 mL
Obtain nasal (midturbinate) swab	X	X					X	
Obtain randomization number and study intervention allocation	X							
Administer study intervention	X	X						

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[d]	←→	←→						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[d]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application						X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviation: e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. Reactogenicity subset participants only.

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy adults.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy adults. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Two SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2-mutant, "heads up," prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein-receptor binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding P2 S.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with possible current clinical COVID-19. All participants are followed for SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 serum neutralizing titers, and COVID-19 illness, including markers of severity.
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of a potentially efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic and antibody testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 serum neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 serum neutralizing titers to the geometric mean of SARS-CoV-2 binding antibody levels at each time point	• SARS-CoV-2 serum neutralizing titers • SARS-CoV-2 anti-S1 binding antibody levels • SARS-CoV-2 anti-RBD binding antibody levels

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

3.2. For Phase 2/3

Objectives	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Objectives	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Exploratory		
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	• SARS-CoV-2 anti-S1 binding antibody levels and/or anti-RBD binding antibody levels • SARS-CoV-2 serum neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• SARS-CoV-2 NVA-specific binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• SARS-CoV-2 anti-S1 binding antibody levels and/or anti-RBD binding antibody levels • SARS-CoV-2 serum neutralizing titers • SARS-CoV-2 NVA-specific binding antibody • SARS-CoV-2 detection by NAAT

This protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy adults.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: 18 to 85 years of age [stratified as ≤55 or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be 18 to 85 years of age, stratified as follows: 18 to 55 years or 56 to 85 years. It is intended that a minimum of 40% of participants will be in the 56- to 85-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the last dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the last dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.0% per year in the placebo group, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 14,643 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, 65 and 85 years, inclusive, or 18 and 85 years, inclusive, at randomization (dependent upon study phase).

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

    Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.

4. Participants who, in the judgment of the investigator, are at risk for acquiring COVID-19.

Informed Consent:

5. Capable of giving personal signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. Previous clinical or microbiological diagnosis of COVID-19.

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - Chronic liver disease
    - Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
    - Resident in a long-term facility
    - BMI >30 kg/m^2
    - Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
   - New or increased cough;
   - New or increased shortness of breath;
   - Chills;
   - New or increased muscle pain;
   - New loss of taste/smell;
   - Sore throat;
   - Diarrhea;
   - Vomiting.
2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.
3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.
4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age]).

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

These 2 investigational RNA vaccine candidates, with the addition of saline placebo, are the 3 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline placebo
Type	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	10-, 20-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWRS). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).

- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. All statistical analyses conducted on Phase 2/3 data while the study is ongoing, that are not in support of the DMC, will be performed by this team. This team will not

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof are not approved

have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).
- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.
- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants).

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria).

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 530 mL for participants in Phase 1 and 125 mL for Phase 2/3 participants. Additionally, 50 mL of blood will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 700 mL during the 24-month study period. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. A local NAAT result will be considered acceptable if it was obtained using:

- An FDA-cleared (including Emergency Use Authorization) assay; or
- An assay that is not FDA-cleared but was conducted in a laboratory that is currently CLIA-certified; or
- An assay performed by a laboratory accredited according to the ISO 15189 standard by a national or regional accreditation body.

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT positive at central laboratory or at a local testing facility (using an acceptable test):
  - Fever;
  - New or increased cough;
  - New or increased shortness of breath;
  - Chills;
  - New or increased muscle pain;
  - New loss of taste or smell;
  - Sore throat;
  - Diarrhea;

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction*;
  - Admission to an ICU;
  - Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive SARS-CoV-2 NVA-binding antibody result in a participant with a prior negative SARS-CoV-2 NVA-binding antibody result

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 serum neutralization assay
- SARS-CoV-2 anti-S1 IgG direct Luminex immunoassay
- SARS-CoV-2 anti-RBD IgG direct Luminex immunoassay
- Nonvaccine antigen (NVA) Ig direct Luminex immunoassay. The NVA will include a SARS-CoV-2 target antigen that is not derived from the S glycoprotein, most likely an antigen derived from the SARS-CoV-2 nucleoprotein.

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~1.70-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2.

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.2.2. Electronic Diary

Participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least 6000 in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Table 3. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the last dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccines SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccines SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccines SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccines SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccines SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccines SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccines SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illness will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

Potential COVID-19 illness events will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccines SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
the european
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 100 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Obtain a nasal (midturbinate) swab (collected by site staff).

- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.

    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary if he/she is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.

- If the participant is part of the reactogenicity subset, ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

    - Fever ≥39.0°C (≥102.1°F).

    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

    - Severe pain at the injection site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.

- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).

- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- If the participant is part of the reactogenicity subset, ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following, he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset. During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory. The result from this swab will be provided to the site once it is available, but this will not be in real time, and cannot be relied upon to direct clinical care. Therefore, the participant should be encouraged to seek care, if appropriate, from his or her usual provider.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
  - Symptoms and signs, including
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
    - Significant acute renal, hepatic, or neurologic dysfunction

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)
- Clinical diagnosis
- Local laboratory COVID-19 test result
- Full blood count
- Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
- Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
- Number and type of any healthcare contact; duration of hospitalization and ICU stay
- Death

- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant and the study site staff will be established. The participant may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant to report whether or not he or she has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant to ascertain why and also to obtain details of any missed events.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will be analyzed by all--available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either $VE_1 > 30\%$ or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

9.2. Sample Size Determination

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

For Phase 2/3, with assumptions of a true VE of 60% after the last dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 11,714 evaluable participants per group or 14,643 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 29,286, based on the assumption of a 1.0% illness rate per year in the placebo group, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

For safety outcomes, Table 4 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 4. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	All eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result 21 days after Dose 1, have blood collection within an appropriate

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Population	Description
	window after Dose 1, and have no other major protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other major protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window, have the efficacy measurement after the last dose of study intervention, and have no other major protocol deviations as determined by the clinician. A major protocol deviation will exclude a participant from the evaluable efficacy population from the date that it occurs through the participant's remaining follow-up.
All-available efficacy	All eligible randomized participants who receive at least 1 vaccination and have the efficacy measurement at any time after Dose 1. All eligible randomized participants who complete 2 vaccination doses and have the efficacy measurement at any time after Dose 2.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody and anti-RBD binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody and anti-RBD binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody and anti-RBD binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 serum neutralizing titer to SARS-CoV-2 anti-S1 binding antibody and SARS-CoV-2 anti-RBD binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody/SARS-CoV-2 anti-RBD binding antibody at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 serum neutralizing titers minus SARS-CoV-2 anti-S1 binding antibody for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody and anti-RBD binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody and anti-RBD binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Endpoint	Statistical Analysis Methods
	• 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with antibody levels ≥ predefined threshold(s) for SARS-CoV-2 serological parameters** For SARS-CoV-2 serum neutralizing titers, SARS-CoV-2 anti-S1 binding antibody levels and/or anti-RBD binding antibody levels, SARS-CoV-2 NVA-specific binding antibody, and SARS-CoV-2 detection by NAAT, percentages (and 2-sided 95% CIs) of participants with antibody levels ≥ predefined threshold(s) will be provided for each investigational product within each group at baseline and each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination The Clopper-Pearson method will be used to calculate the CIs. **Percentage of participants with the immune response (non-S) to SARS-CoV-2 for SARS-CoV-2 NVA-specific binding antibody at the time points when data are available** The Clopper-Pearson method will be used to calculate the CIs. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Endpoint	Statistical Analysis Methods
	RCDCs for immunogenicity results Empirical RCDCs will be provided for SARS-CoV-2 serum neutralizing titers, SARS-CoV-2 S1-specific binding antibody, and RBD-specific binding antibody after Dose 1 and after Dose 2.

9.4.2. Efficacy Analyses

The statistical analysis of efficacy will be based on the evaluable efficacy population (primary analysis) and the all-available efficacy population as defined in Section 9.3.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group 7 days after the last dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in participants with and without evidence of infection before vaccination for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group after 7 days after the last dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Endpoint	Statistical Analysis Methods
	The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values; details will be provided in the SAP.
Secondary	**Ratio of confirmed severe COVID-19 illness per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** **Ratio of confirmed severe COVID-19 illness per 1000 person-years of follow-up for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints will be evaluated descriptively with 95% CIs. **Ratio of confirmed COVID-19 illness (according to the CDC-defined symptoms) per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** **Ratio of confirmed COVID-19 illness (according to the CDC-defined symptoms) per 1000 person-years of follow-up in participants with and without evidence of infection before vaccination for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms after 7 days after the last dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[9] Missing efficacy data will not be imputed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Endpoint	Statistical Analysis Methods
	from Dose 1 to 6 months after last dose will be provided for each vaccine group. The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory	N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 serum neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the SARS-CoV-2 S1-specific binding antibody level at the postvaccination time point to the corresponding antibody level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the SARS-CoV-2 RBD-specific binding antibody level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs are planned and will be performed by an unblinded statistical team after accrual of 32, 62, 92, and 120 cases. At each IA:

- VE for the first primary objective will be evaluated . Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 5 illustrates the boundary for efficacy and futility if IAs are performed after accrual of 32 62, 92, and 120 cases in participants without evidence of infection before vaccination.

Table 5. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (19:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 6 and Table 7.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
emea-h-c-pi
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Table 6. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.035	<0.001	0.003

Table 7. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the last dose of investigational product onwards.

After the primary objectives are met, the secondary VE endpoints (confirmed severe COVID-19 in participants without evidence of infection before vaccination and confirmed severe COVID-19 in all participants) will be evaluated sequentially, by the same method used for the primary VE endpoint evaluation. Success thresholds for secondary VE will be appropriately chosen to control overall Type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo) in Phase 2/3.
- Safety and immunogenicity data through 1 month after Dose 2 from the first 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3.
- IAs for efficacy at 32, 62, 92, and 120 cases and futility at 32, 62, and 92 cases.
- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.
- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met
- Review of safety and/or immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and serum neutralizing titers, and the ratio between them, will also be submitted to the FDA for review

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 8).

Table 8. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Table 8. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. • Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccines SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccines SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccines SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccines SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccines SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccines SAE Report Form
• Facsimile transmission of the Vaccines SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccines SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccines SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use application
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration

This document cannot be used to support a marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Abbreviation	Term
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N/A	not applicable
NAAT	nucleic acid amplification test
non-S	nonspike protein
NVA	nonvaccine antigen
P2 S	SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Abbreviation	Term
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs at 32, 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 9 and Table 10, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

This document cannot be used to support any marketing authorisation application and any extension of variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Table 9. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 10. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)
This document cannot be used to support and marketing authorisation application and any extensions or variations thereof
ema.europa.eu

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.

4 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

5 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

6 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

7 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine. 2019;37(25):3326-34.

8 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

9 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

10 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 5, Clean copy, 24 July 2020
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY ADULTS

Signed By:	Date(GMT)	Signing Capacity
PPD	24-Jul-2020 13:03:31	Business Line Approver
PPD	24-Jul-2020 13:05:32	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1947b6a02\Approved\Approved On: 24-Jul-2020 13:05 (GMT)

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY ADULTS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation, and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19 disease.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

		candidates have been removed from the protocol. • To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age In addition:

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

		• Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial • Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

		• Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

TABLE OF CONTENTS

LIST OF TABLES 12
1. PROTOCOL SUMMARY 13
1.1. Synopsis 13
1.2. Schema 20
1.3. Schedule of Activities 21
1.3.1. Stage 1 Sentinel Cohorts 21
1.3.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts 26
1.3.3. Stage 3 Cohort(s) 29
2. INTRODUCTION 31
2.1. Study Rationale 31
2.2. Background 31
2.2.1. Clinical Overview 32
2.3. Benefit/Risk Assessment 32
2.3.1. Risk Assessment 33
2.3.2. Benefit Assessment 34
2.3.3. Overall Benefit/Risk Conclusion 34
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 34
3.1. For Stages 1 and 2 34
3.2. For Stage 3 36
4. STUDY DESIGN 38
4.1. Overall Design 38
4.1.1. Stage 1 38
4.1.2. Stage 2 40
4.1.3. Stage 3 40
4.2. Scientific Rationale for Study Design 41
4.3. Justification for Dose 41
4.4. End of Study Definition 42
5. STUDY POPULATION 42
5.1. Inclusion Criteria 43

5.2. Exclusion Criteria....43
5.3. Lifestyle Considerations....46
5.3.1. Contraception....46
5.4. Screen Failures....46
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration....46
6. STUDY INTERVENTION....47
6.1. Study Intervention(s) Administered....50
6.1.1. Administration....50
6.2. Preparation/Handling/Storage/Accountability....51
6.2.1. Preparation and Dispensing....52
6.3. Measures to Minimize Bias: Randomization and Blinding....52
6.3.1. Allocation to Study Intervention....52
6.3.2. Blinding of Site Personnel....52
6.3.3. Blinding of the Sponsor....53
6.3.4. Breaking the Blind....53
6.4. Study Intervention Compliance....53
6.5. Concomitant Therapy....53
6.5.1. Prohibited During the Study....54
6.5.2. Permitted During the Study....54
6.6. Dose Modification....55
6.7. Intervention After the End of the Study....55
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL....55
7.1. Discontinuation of Study Intervention....55
7.2. Participant Discontinuation/Withdrawal From the Study....55
7.2.1. Withdrawal of Consent....56
7.3. Lost to Follow-up....57
8. STUDY ASSESSMENTS AND PROCEDURES....57
8.1. Efficacy and/or Immunogenicity Assessments....58
8.1.1. Biological Samples....61
8.2. Safety Assessments....61

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

8.2.1. Clinical Safety Laboratory Assessments (Sentinel-Cohort Participants Only) 61
8.2.2. Electronic Diary 62
8.2.2.1. Grading Scales 62
8.2.2.2. Local Reactions 63
8.2.2.3. Systemic Events 63
8.2.2.4. Fever 64
8.2.2.5. Antipyretic Medication 65
8.2.3. Stopping Rules 65
8.2.3.1. Randomization and Vaccination After a Stopping Rule Is Met 67
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 Disease 67
8.2.5. Pregnancy Testing 67
8.3. Adverse Events and Serious Adverse Events 68
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 68
8.3.1.1. Reporting SAEs to Pfizer Safety 69
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 69
8.3.2. Method of Detecting AEs and SAEs 69
8.3.3. Follow-up of AEs and SAEs 69
8.3.4. Regulatory Reporting Requirements for SAEs 70
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 70
8.3.5.1. Exposure During Pregnancy 70
8.3.5.2. Exposure During Breastfeeding 72
8.3.5.3. Occupational Exposure 72
8.3.6. Cardiovascular and Death Events 72
8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 72
8.3.8. Adverse Events of Special Interest 73
8.3.8.1. Lack of Efficacy 73
8.3.9. Medical Device Deficiencies 73
8.3.10. Medication Errors 73

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

8.4. Treatment of Overdose 74
8.5. Pharmacokinetics 74
8.6. Pharmacodynamics 74
8.7. Genetics 74
8.8. Biomarkers 74
8.9. Immunogenicity Assessments 74
8.10. Health Economics 75
8.11. Study Procedures 75
8.11.1. Stage 1 Sentinel Cohorts 75
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 75
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 76
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 78
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 79
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 80
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 83
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 84
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 85
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 4) 86
8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4) 86
8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4) 87
8.11.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts 87
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 87
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1) 89
8.11.2.3. Visit 3 – 2-Week Follow-up Visit: (12 to 16 Days After Visit 2) 91

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

8.11.2.4. Visit 4 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 2) 92
8.11.2.5. Visit 5 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 2) 92
8.11.2.6. Visit 6 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2) 93
8.11.2.7. Visit 7 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2) 93
8.11.3. Stage 3 Cohort(s) 94
8.11.3.1. Visit 1 – Vaccination 1: (Day 1) 94
8.11.3.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1) 96
8.11.3.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2) 98
8.11.3.4. Visit 4 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 2) 99
8.11.3.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2) 99
8.11.3.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2) 100
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 100
8.13. COVID-19 Disease Surveillance (All Participants) 101
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 102
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit) 103
8.14. Communication and Use of Technology 103
9. STATISTICAL CONSIDERATIONS 104
9.1. Estimands and Statistical Hypotheses 104
9.1.1. Estimands 104
9.1.2. Statistical Hypotheses 105
9.2. Sample Size Determination 105
9.3. Analysis Sets 106
9.4. Statistical Analyses 107
9.4.1. Immunogenicity Analyses 107

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

9.4.2. Efficacy Analyses 112
9.4.3. Safety Analyses 114
9.4.4. Other Analyses....115
9.5. Interim Analyses 115
9.5.1. Analysis Timing....118
9.6. Data Monitoring Committee or Other Independent Oversight Committee....118
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 120
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 120
10.1.1. Regulatory and Ethical Considerations 120
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP....120
10.1.2. Informed Consent Process 121
10.1.3. Data Protection 122
10.1.4. Dissemination of Clinical Study Data 122
10.1.5. Data Quality Assurance 123
10.1.6. Source Documents....125
10.1.7. Study and Site Start and Closure 125
10.1.8. Sponsor's Qualified Medical Personnel 126
10.2. Appendix 2: Clinical Laboratory Tests 127
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 129
10.3.1. Definition of AE 129
10.3.2. Definition of SAE 130
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs....132
10.3.4. Reporting of SAEs....135
10.4. Appendix 4: Contraceptive Guidance 136
10.4.1. Male Participant Reproductive Inclusion Criteria 136
10.4.2. Female Participant Reproductive Inclusion Criteria....136
10.4.3. Woman of Childbearing Potential 137
10.4.4. Contraception Methods....138
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 140

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.6. Appendix 6: Abbreviations 142
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 146
11. REFERENCES 148

LIST OF TABLES

Table 1. Potential Groups in Stage 1 48
Table 2. Local Reaction Grading Scale 63
Table 3. Systemic Event Grading Scale 64
Table 4. Scale for Fever 65
Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 106
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility 116
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses 117
Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall 117
Table 9. Laboratory Abnormality Grading Scale 127
Table 10. For 2 to 20 Cases of Severe COVID-19, Probability of Observing This Number or More of Severe Cases in the Vaccine Group at a Range of True Adverse Ratios From 1:1 to 4:1 146

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or antiviral drugs to treat COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 3 antigens: the SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein (P2 S) (version 9), a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5), or a membrane-anchored trimerized SARS-CoV-2 RBD. The 3 SARS-CoV-2 vaccine candidates that may be tested in this study are therefore:

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S;

BNT162b3 (variant RBP020.8): a modRNA encoding a membrane-anchored RBD.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and efficacy of these prophylactic BNT162 vaccines against COVID-19.

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

It is expected that the various candidate vaccines may not all be available from the start of the study, in which case they will be rolled into the study in a consecutive fashion as they are released. A Phase 1/2 study of the same vaccine candidates (BNT162-01), conducted in Germany by BioNTech in adults 18 to 55 years of age, started in April 2020.
Study C4591001 is designed to complement and expand upon the German study and confirm the optimal vaccine candidate(s), dose level(s), number of doses, and schedule of administration.

Objectives, Estimands, and Endpoints

For Stages 1 and 2

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, in sentinel cohorts from Stage 1, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: ***Stage 1 Sentinel Cohorts:*** 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts:*** 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2	

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 serum neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 serum neutralizing titers to the geometric mean of SARS-CoV-2–binding antibody levels at each time point	• SARS-CoV-2 serum neutralizing titers • SARS-CoV-2 anti-S1 binding antibody levels • SARS-CoV-2 anti-RBD binding antibody levels

For Stage 3

Objectives	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacies of individual prophylactic BNT162 vaccines against confirmed COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To evaluate the efficacies of individual prophylactic BNT162 vaccines against confirmed COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Objectives	Estimands	Endpoints
Primary Safety		
To define the safety profiles of individual prophylactic BNT162 vaccines in the first 360 participants randomized in Stage 3	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profiles of individual prophylactic BNT162 vaccines in all participants randomized in Stage 3	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
Secondary Efficacy		
To evaluate the efficacies of individual prophylactic BNT162 vaccines against confirmed severe COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence of past SARS-CoV-2 infection
To evaluate the efficacies of individual prophylactic BNT162 vaccines against confirmed severe COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacies of individual prophylactic BNT162 vaccines against confirmed COVID-19 (according to the CDC-defined symptoms) in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To describe the efficacies of individual prophylactic BNT162 vaccines against confirmed COVID-19 (according to the CDC-defined symptoms) in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emanuele.pera@eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Objectives	Estimands	Endpoints
Secondary Immunogenicity		
To evaluate the immune response over time to BNT162 prophylactic vaccines and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	• SARS-CoV-2 anti-S1 binding antibody levels and/or anti-RBD binding antibody levels • SARS-CoV-2 serum neutralizing titers
Exploratory		
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• SARS-CoV-2 NVA-specific binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• SARS-CoV-2 anti-S1 binding antibody levels and/or anti-RBD binding antibody levels • SARS-CoV-2 serum neutralizing titers • SARS-CoV-2 NVA-specific binding antibody • SARS-CoV-2 detection by NAAT

Overall Design

This is a Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, and vaccine candidate–selection study in healthy adults.

The study will evaluate the safety, tolerability, immunogenicity, and efficacy of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19:

- As a 2-dose (separated by 21 or 60 days) or single-dose schedule
- At various different dose levels
- In 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age])

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study consists of 3 stages. Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

expanded-cohort stage; and Stage 3: an efficacy stage. These stages, and the progression between them, are detailed in the schema (Section 1.2).

A vaccine candidate/dose level that, in Stage 1, has an established dose level and immunization schedule based on induction of an immune response in the sentinel evaluation, including neutralizing antibodies, and is expected to be associated with protection against COVID-19, can progress directly into Stage 3.

Vaccine candidate(s) that have preliminary evidence to support a dose and schedule and to show that the candidate is safe and has evidence of vaccine-elicited antibody, but require further safety and immunogenicity data to support progression to Stage 3, can progress to Stage 2.

Number of Participants

Each group in Stage 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this stage, assuming 2 dose levels are selected following the initial dose escalation, up to 42 potential groups are foreseen; if all groups are fully enrolled, this corresponds to a total of 630 participants.

Each group in Stage 2 will comprise 225 participants (180 receiving active vaccine and 45 receiving placebo). The total number of participants to be enrolled in this stage depends on the number of groups to be pursued.

Each vaccine candidate/dose level selected for Stage 3 will comprise 14,643 vaccine recipients. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study may evaluate single-dose and 2-dose (separated by 21 or 60 days) schedules of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg
- BNT162b3 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding a membrane-anchored RBD): 10 µg, 20 µg, 30 µg

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Stage 1 and Stage 2 dosing arms that are not evaluated in Stage 3.

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The study sample size for the first 2 stages of the study is not based on any statistical hypothesis testing.

For the third stage, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 29,286 participants (14,643 vaccine recipients), based on the assumption of a 1.0% per year incidence in the placebo group, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Stage 3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the number of candidate vaccines evaluated, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

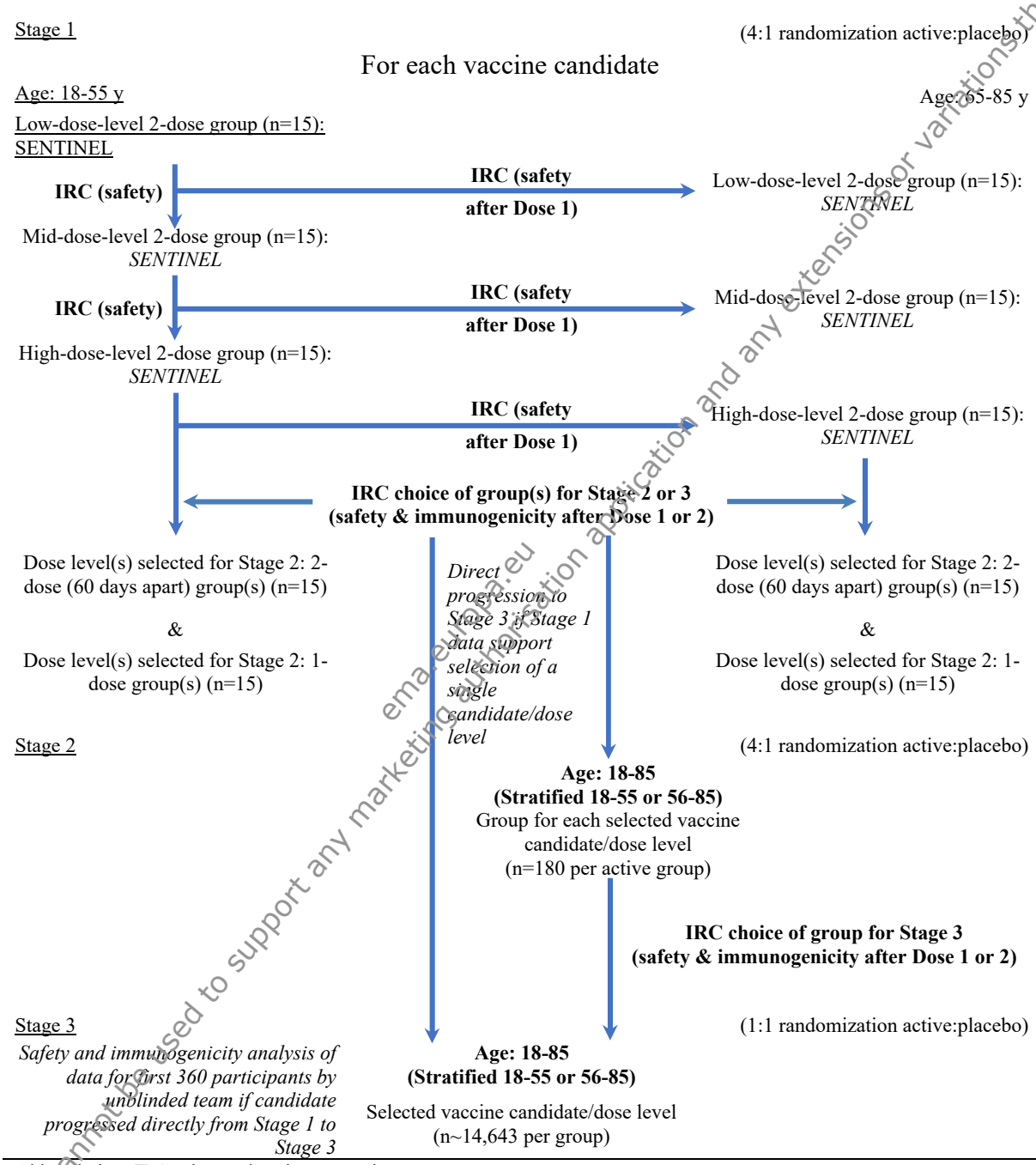
The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (sentinel cohorts only), for each vaccine group. A 3-tier approach will be used to summarize AEs.

The secondary immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 serum neutralizing titers, SARS-CoV-2 anti-S1 binding antibody levels, and anti-RBD binding antibody levels at the various time points.

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.2. Schema



Abbreviation: IRC = internal review committee.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

090177e1941f5edeApproved\Approved On: 01-Jul-2020 13:44 (GMT)

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Stage 1 Sentinel Cohorts

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						

This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[c]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								

090177e1941f5edeApproved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL	~50 mL	~50 mL		~50 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X								
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X											
Provide thermometer and measuring device		X			X								
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►	◄	►							

090177e1941f5edeApproved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application											X		

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in in each sentinel group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e1941f5edeApproved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 7 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	1	2	3	4	5	6	7	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[b]**	**12 to 16 Days After Visit 2**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X								
Assign participant number	X								
Obtain demography and medical history data	X								
Perform physical examination	X								
Measure vital signs	X								
Perform urine pregnancy test (if appropriate)	X	X							
Collect nonstudy vaccine information	X	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X	X
Confirm eligibility	X	X							
Measure temperature (body)	X	X							
Review temporary delay criteria	X	X							
Confirm use of contraceptives (if appropriate)	X	X	X	X					
Obtain randomization number and study intervention allocation	X								

090177e1941f5edeApproved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	7	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[b]**	**12 to 16 Days After Visit 2**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collect blood sample for immunogenicity assessment	~25 mL	~25 mL	~25 mL	~25 mL	~25 mL	~25 mL	~25 mL		~50 mL
Obtain nasal (midturbinate) swab	X	X						X	
Administer study intervention	X	X							
Assess acute reactions for at least 30 minutes after study intervention administration	X	X							
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X								
Provide participant with thermometer and measuring device	X	X							
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	←→	←→							
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X	X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application							X		

090177e1941f5edeApproved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	7	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[b]**	**12 to 16 Days After Visit 2**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)								X	X

Abbreviation: e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The window for Visit 2 is dependent on the dosing schedule for the assigned group.

090177e1941f5edeApproved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Stage 3 Cohort(s)

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	1	2	3	4	5	6	Unplanned 7	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[b]**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
Measure height and weight	X							
Perform urine pregnancy test (if appropriate)	X	X						
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Measure temperature (body)	X	X						
Review temporary delay criteria	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Obtain randomization number and study intervention allocation	X							
Collect blood sample for immunogenicity assessment	~25 mL		~25 mL	~25 mL	~25 mL	~25 mL		~50 mL
Obtain nasal (midturbinate) swab	X	X					X	
Administer study intervention	X	X						

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu

090177e1941f5edeApproved\Approved On: 01-Jul-2020 13:44 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[b]**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[d]	◄——►	◄——►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[d]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application						X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviation: e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The window for Visit 2 is dependent on the dosing schedule(s) selected for Stage 3.
c. Including, if indicated, a physical examination.
d. Reactogenicity subset participants only.

090177e1941f5edeApproved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy adults.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, immunogenicity, and efficacy of 3 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19 in healthy adults. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or antiviral drugs to treat COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with

traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Three SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) may be evaluated in this study. Each vaccine candidate expresses 1 of 3 antigens: the SARS-CoV-2 full-length, P2-mutant, "heads up," prefusion spike glycoprotein (P2 S) (version 9), a trimerized SARS-CoV-2 spike glycoprotein-receptor binding domain (RBD) (version 5), or a membrane-anchored trimerized SARS-CoV-2 RBD. The 3 SARS-CoV-2 vaccine candidates that may be tested in this study are therefore:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.
- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding P2 S.
- **BNT162b3** (variant RBP020.8): nucleoside-modified messenger RNA (modRNA) as above, but encoding a membrane-anchored RBD.

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The study design includes the use of sentinel cohorts and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogeniety e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place for sentinel cohorts. The first 5 sentinel-cohort participants in each group will be observed for 4 hours after vaccination to assess any immediate AEs.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The study design includes the use of sentinel cohorts and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC and DMC will also review safety data throughout the study. Stopping rules are also in place for sentinel cohorts. The first 5 sentinel-cohort participants in each group will be observed for 4 hours after vaccination to assess any immediate AEs.
Potential for COVID-19 disease enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Stages 1 and 2 exclude participants with likely previous or current COVID-19. In Stage 3, temporary delay criteria defer vaccination of participants with possible current clinical COVID-19. All participants are followed for SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 serum neutralizing titers, and COVID-19 illness, including markers of severity.
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e1941f5edeApproved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of a potentially efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic and antibody testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Stages 1 and 2

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, in sentinel cohorts from Stage 1, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: ***Stage 1 Sentinel Cohorts:*** 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts:*** 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 serum neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 serum neutralizing titers to the geometric mean of SARS-CoV-2 binding antibody levels at each time point	• SARS-CoV-2 serum neutralizing titers • SARS-CoV-2 anti-S1 binding antibody levels • SARS-CoV-2 anti-RBD binding antibody levels

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

3.2. For Stage 3

Objectives	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacies of individual prophylactic BNT162 vaccines against confirmed COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To evaluate the efficacies of individual prophylactic BNT162 vaccines against confirmed COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profiles of individual prophylactic BNT162 vaccines in the first 360 participants randomized in Stage 3	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profiles of individual prophylactic BNT162 vaccines in all participants randomized in Stage 3	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
Secondary Efficacy		
To evaluate the efficacies of individual prophylactic BNT162 vaccines against confirmed severe COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence of past SARS-CoV-2 infection

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Objectives	Estimands	Endpoints
To evaluate the efficacies of individual prophylactic BNT162 vaccines against confirmed severe COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacies of individual prophylactic BNT162 vaccines against confirmed COVID-19 (according to the CDC-defined symptoms) in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To describe the efficacies of individual prophylactic BNT162 vaccines against confirmed COVID-19 (according to the CDC-defined symptoms) in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Secondary Immunogenicity		
To evaluate the immune response over time to BNT162 prophylactic vaccines and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	• SARS-CoV-2 anti-S1 binding antibody levels and/or anti-RBD binding antibody levels • SARS-CoV-2 serum neutralizing titers
Exploratory		
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• SARS-CoV-2 NVA-specific binding antibody
To describe the serological responses to the BNT vaccine candidates in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• SARS-CoV-2 anti-S1 binding antibody levels and/or anti-RBD binding antibody levels • SARS-CoV-2 serum neutralizing titers • SARS-CoV-2 NVA-specific binding antibody • SARS-CoV-2 detection by NAAT

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, and vaccine candidate–selection study in healthy adults.

The study will evaluate the safety, tolerability, immunogenicity, and efficacy of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19:

- As a 2-dose (separated by 21 or 60 days) or single-dose schedule
- At various different dose levels
- In 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age])

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study consists of 3 stages. Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3: an efficacy stage. These stages, and the progression between them, are detailed in the schema (Section 1.2).

Stages 1 and 2 represent a Phase 1/2a assessment of a number of BNT162 vaccine candidates and dose levels. Stage 3 is a seamless Phase 2b/3 assessment of one (or possibly more) selected BNT162 vaccine candidate/dose level, powered to demonstrate efficacy.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Stage 1 and Stage 2.

4.1.1. Stage 1

Each group (vaccine candidate/dose level/age group/number of doses) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo. On Day 22, those in 2-dose groups will receive the same vaccine they received on Day 1; for those in single-dose groups, all will receive placebo. Full details of all potential groups in Stage 1 may be found in Table 1.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

For each vaccine candidate/dose level/age group, the 15 participants randomized into each 2-dose group will comprise a sentinel cohort, to which the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since all candidates are based upon the same RNA platform, dose escalation for the second and subsequent candidate(s) studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

Once the IRC has selected a vaccine candidate/dose level to proceed into a later stage, for each age cohort, 2 additional groups may be enrolled into Stage 1 for that vaccine candidate/dose level:

- A 2-dose group, with the 2 doses administered 60 days apart rather than 21
- A 1-dose group

In this stage, assuming 2 dose levels are selected following the initial dose escalation, up to 42 potential groups are foreseen; if all groups are fully enrolled, this corresponds to a total of 630 participants.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

A vaccine candidate/dose level that, in Stage 1, has an established dose level and immunization schedule based on induction of an immune response in the sentinel evaluation, including neutralizing antibodies, and is expected to be associated with protection against COVID-19, can progress directly into Stage 3.

Vaccine candidate(s) that have preliminary evidence to support a dose and schedule and to show that the candidate is safe and has evidence of vaccine-elicited antibody, but require further safety and immunogenicity data to support progression to Stage 3, can progress to Stage 2.

Since BNT162b1 and BNT162b3 are so similar, data from BNT162b1 may be used to support progression of BNT162b3 into either Stage 2 or Stage 3.

4.1.2. Stage 2

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 or more groups (vaccine candidate/dose level) may be selected to proceed into Stage 2. Participants in this stage will be 18 to 85 years of age, stratified as follows: 18 to 55 or 56 to 85 years. It is targeted to enroll approximately equal numbers of participants in the 2 age strata. Commencement of each age stratum will be dependent upon satisfactory safety and immunogenicity data from the 18- to 55-year and 65- to 85-year groups from Stage 1, respectively. It is therefore possible that the 2 age strata may not start concurrently.

In each group selected for Stage 2, it is intended that 225 participants will be randomized in a 4:1 ratio to receive active vaccine (180 participants) or placebo (45 participants).

4.1.3. Stage 3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 or more group(s) may be selected to proceed into Stage 3. Participants in this stage will be 18 to 85 years of age, stratified as follows: 18 to 55 years or 56 to 85 years. As in Stage 2, it is targeted to enroll approximately equal numbers of participants in the 2 age strata and it is possible that the 2 age strata may not start concurrently.

Stage 3 is event-driven. Under the assumption of a true VE rate of ≥60%, and using an efficacy criterion that requires the LL (of the alpha-adjusted CI for VE) to be >30%, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the last dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to meet the primary objective. The total number of participants enrolled in Stage 3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the number of candidate vaccines evaluated, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.0% per year in the placebo group, an estimated 20% nonevaluable rate, and 1:1 randomization, each vaccine candidate/dose level selected for

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Stage 3 is expected to comprise approximately 14,643 vaccine recipients per group. This is the number of participants initially targeted for Stage 3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

For a vaccine candidate/dose level that progresses directly from Stage 1 to Stage 3, the first 360 participants enrolled (180 to active vaccine and 180 to placebo) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 21 days after Dose 1 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Stage 1 and Stage 2 dosing arms that are not evaluated in Stage 3.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data are not currently available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Stages 1 and 2 in groups that do not proceed to Stage 3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, 65 and 85 years, inclusive, or 18 and 85 years, inclusive, at randomization (dependent upon study stage).

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.

Informed Consent:

4. Capable of giving personal signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

4. Receipt of medications intended to prevent COVID-19.

5. **Stages 1 and 2 only:** Previous clinical or microbiological diagnosis of COVID-19.

6. **Sentinel participants in Stage 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - Chronic liver disease
    - Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
    - Resident in a long-term facility
    - BMI >30 kg/m^2
    - Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Sentinel participants in Stage 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. **Sentinel participants in Stage 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for sentinel participants in Stage 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Sentinel participants in Stage 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Sentinel participants in Stage 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

19. **Sentinel participants in Stage 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Sentinel participants in Stage 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Sentinel participants in Stage 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Other Exclusions:

22. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.

3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study may evaluate 2-dose (separated by 21 or 60 days) and single-dose schedules of various different dose levels of 3 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age]).

These 3 investigational RNA vaccine candidates, with the addition of saline placebo, are the 3 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg
- BNT162b3 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding a membrane-anchored RBD): 10 µg, 20 µg, 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

A list of all potential groups in the Stage 1 are shown in Table 1. Each of these groups may or may not progress to the later stages of the study.

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
2-Dose Groups (Sentinel Cohorts)			**Day 1**			**Day 22**		
b1-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	10 µg	(n=12) (n=3)	BNT162b1 Placebo	10 µg	(n=12) (n=3)
b1-20-2-Y (Sentinel) [modRNA 20 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	20 µg	(n=12) (n=3)	BNT162b1 Placebo	20 µg	(n=12) (n=3)
b1-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	30 µg	(n=12) (n=3)	BNT162b1 Placebo	30 µg	(n=12) (n=3)
b1-100-2-Y (Sentinel) [modRNA 100 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	100 µg	(n=12) (n=3)	BNT162b1 Placebo	100 µg	(n=12) (n=3)
b2-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	10 µg	(n=12) (n=3)	BNT162b2 Placebo	10 µg	(n=12) (n=3)
b2-20-2-Y (Sentinel) [modRNA 20 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	20 µg	(n=12) (n=3)	BNT162b2 Placebo	20 µg	(n=12) (n=3)
b2-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	30 µg	(n=12) (n=3)	BNT162b2 Placebo	30 µg	(n=12) (n=3)
b3-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b3 Placebo	10 µg	(n=12) (n=3)	BNT162b3 Placebo	10 µg	(n=12) (n=3)
b3-20-2-Y (Sentinel) [modRNA 20 µg (2 doses)]	15	18 to 55	BNT162b3 Placebo	20 µg	(n=12) (n=3)	BNT162b3 Placebo	20 µg	(n=12) (n=3)
b3-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b3 Placebo	30 µg	(n=12) (n=3)	BNT162b3 Placebo	30 µg	(n=12) (n=3)
b1-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	10 µg	(n=12) (n=3)	BNT162b1 Placebo	10 µg	(n=12) (n=3)
b1-20-2-O (Sentinel) [modRNA 20 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	20 µg	(n=12) (n=3)	BNT162b1 Placebo	20 µg	(n=12) (n=3)
b1-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	30 µg	(n=12) (n=3)	BNT162b1 Placebo	30 µg	(n=12) (n=3)
b2-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	10 µg	(n=12) (n=3)	BNT162b2 Placebo	10 µg	(n=12) (n=3)
b2-20-2-O (Sentinel) [modRNA 20 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	20 µg	(n=12) (n=3)	BNT162b2 Placebo	20 µg	(n=12) (n=3)
b2-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	30 µg	(n=12) (n=3)	BNT162b2 Placebo	30 µg	(n=12) (n=3)
b3-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b3 Placebo	10 µg	(n=12) (n=3)	BNT162b3 Placebo	10 µg	(n=12) (n=3)
b3-20-2-O (Sentinel) [modRNA 20 µg (2 doses)]	15	65 to 85	BNT162b3 Placebo	20 µg	(n=12) (n=3)	BNT162b3 Placebo	20 µg	(n=12) (n=3)
b3-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b3 Placebo	30 µg	(n=12) (n=3)	BNT162b3 Placebo	30 µg	(n=12) (n=3)

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
Single-Dose Groups			**Day 1**			**Day 22**		
b1-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b2-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b3-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b3 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b1-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b2-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b3-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b3 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
2-Dose Groups (Longer Schedule)			**Day 1**			**Day 61**		
b1-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b1 Placebo	TBD	(n=12) (n=3)	BNT162b1 Placebo	TBD	(n=12) (n=3)
b2-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b2 Placebo	TBD	(n=12) (n=3)	BNT162b2 Placebo	TBD	(n=12) (n=3)
b3-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b3 Placebo	TBD	(n=12) (n=3)	BNT162b3 Placebo	TBD	(n=12) (n=3)
b1-x-2L-O [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162b1 Placebo	TBD	(n=12) (n=3)	BNT162b1 Placebo	TBD	(n=12) (n=3)
b2-x-2L-O [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162b2 Placebo	TBD	(n=12) (n=3)	BNT162b2 Placebo	TBD	(n=12) (n=3)
b3-x-2L-O [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162b3 Placebo	TBD	(n=12) (n=3)	BNT162b3 Placebo	TBD	(n=12) (n=3)

Abbreviations: modRNA = nucleoside-modified messenger ribonucleic acid; TBD = to be determined.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b3 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline placebo
Type	Vaccine	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	10-, 20-, 30-µg	10-, 20-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

6.1.1. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Stage 1 sentinel-cohort participants, Visits 1 and 2 for all other participants) in accordance with the study's SoA. The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emanuscope.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Stage 1 and in Stage 2. Sponsor staff will be blinded to study intervention allocation in Stage 3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study.

Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate). Unblinded clinician(s) who are not direct members of the study team will review unblinded protocol deviations. All statistical analyses conducted on Stage 3 data while the study is ongoing will be performed by an unblinded statistical team.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Stage 1 sentinel cohorts, Visit 5 for Stage 1 nonsentinel cohorts and Stage 2 participants, and Visit 4 for Stage 3 participants).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

- In addition, for participants enrolled in the Stage 1 sentinel cohorts, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 for Stage 1 sentinel cohorts, Visit 4 for Stage 1 nonsentinel cohorts and Stage 2 participants, and Visit 3 for Stage 3 participants).

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Stage 1 sentinel cohorts.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Stage 1 sentinel cohorts – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria).

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
email.ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, she/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 530 mL for participants in the Stage 1 sentinel cohorts; 350 mL for participants in the Stage 1 nonsentinel cohorts and Stage 2 participants; and 125 mL for Stage 3 participants. Additionally, 50 mL of blood will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Select participants in the sentinel cohorts of Stage 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 700 mL during the 24-month study period. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. A local NAAT result will be considered acceptable if it was obtained using:

- An FDA-cleared (including Emergency Use Authorization) assay; or
- An assay that is not FDA cleared but was conducted in a laboratory that is currently CLIA certified; or
- An assay performed by a laboratory accredited according to the ISO 15189 standard by a national or regional accreditation body.

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof is europa.eu

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT positive at central laboratory or at a local testing facility (using an acceptable test):
  - Fever;
  - New or increased cough;
  - New or increased shortness of breath;
  - Chills;
  - New or increased muscle pain;
  - New loss of taste or smell;
  - Sore throat;
  - Diarrhea;
  - Vomiting.

  The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

  - Fatigue;
  - Headache;
  - Nasal congestion or runny nose;
  - Nausea.
- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction*;
- Admission to an ICU;
- Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

* If a NAAT-confirmed case in Stage 3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by 3 medically qualified Pfizer staff members to assess whether the criterion is met; the majority opinion will prevail.

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive SARS-CoV-2 NVA-binding antibody result in a participant with a prior negative SARS-CoV-2 NVA-binding antibody result

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 serum neutralization assay
- SARS-CoV-2 anti-S1 IgG direct Luminex immunoassay
- SARS-CoV-2 anti-RBD IgG direct Luminex immunoassay
- Nonvaccine antigen (NVA) Ig direct Luminex immunoassay. The NVA will include a SARS-CoV-2 target antigen that is not derived from the S glycoprotein, most likely an antigen derived from the SARS-CoV-2 nucleoprotein.

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Stage 1 sentinel cohorts (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in the sentinel cohorts of Stage 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Stage 1 sentinel group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2.

8.2.1. Clinical Safety Laboratory Assessments (Sentinel-Cohort Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.2. Electronic Diary

Participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Stages 1 and 2, and a subset of at least 6000 in Stage 3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 2. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 2.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 3.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 4.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 4. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Stopping Rules

The following stopping rules are in place for all Stage 1 sentinel-cohort participants, based on review of AE data and e-diary reactogenicity data. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during the Stage 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19 disease.

A separate stopping rule will apply in Stage 3 for enhanced COVID-19 disease. At the time of each IA, the numbers of severe cases in the vaccine and placebo groups will be assessed. If there are more severe cases in the vaccine group than in the placebo group, the DMC will be advised to recommend that enrollment be stopped if the probability of the adverse split being observed is <1%, assuming that severe cases are truly evenly split. Further details can be found in Section 10.7. If enrollment is stopped, second doses will still be administered, and follow-up will continue. If the probability is ≥1% and <11%, the DMC will be advised to request probability to be recalculated as each additional severe case is accrued.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeurope.ru

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

8.2.3.1. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC and DMC have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 Disease

As this is a sponsor open-label study during Stages 1 and 2, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment.

Participants in all stages of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13). All NAAT-confirmed cases in Stages 1 and 2 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Stage 3, the unblinded statistical team, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review. Since the DMC is able to review unblinded information, it will also be able to compare cases in active vaccine and placebo recipients in Stage 3 (when sponsor staff will be blinded).

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Stage 1 sentinel-cohort participants, Visit 4 for Stage 1 nonsentinel participants and Stage 2 participants, and Visit 3 for Stage 3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Stage 1 sentinel-cohort participants, Visit 5 for Stage 1 non–sentinel-cohort participants and Stage 2 participants, and Visit 4 for Stage 3 participants).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccines SAE Report Form.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccines SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccines SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccines SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccines SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccines SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccines SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccines SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

8.11.1. Stage 1 Sentinel Cohorts

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- The first 5 participants vaccinated in each Stage 1 sentinel group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
    - Severe pain at the injection site.

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Discuss contraceptive use as described in Section 10.4.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

- Fever ≥39.0°C (≥102.1°F).
- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant (select participants only, details will be provided by the Sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)

The window for Visit 2 is dependent on the dosing schedule for the assigned group.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (≥20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 2-Week Follow-up Visit: (12 to 16 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

8.11.2.4. Visit 4 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.5. Visit 5 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.7. Visit 7 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

8.11.3. Stage 3 Cohort(s)

8.11.3.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 disease surveillance) and provide instructions on its use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary if he/she is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- If the participant is part of the reactogenicity subset, ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
    - Severe pain at the injection site.
    - Any severe systemic event.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.3.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)

The window for Visit 2 is dependent on the dosing schedule(s) selected for Stage 3.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).

- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- If the participant is part of the reactogenicity subset, ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.3.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.3.4. Visit 4 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.3.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.11.3.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Disease Surveillance (All Participants)

If a participant experiences any of the following, he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset. During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit is expected to involve the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory. The result from this swab will be provided to the site once it is available, but this will not be in real time, and cannot be relied upon to direct clinical care. Therefore, the participant should be encouraged to seek care, if appropriate, from his or her usual provider.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
  - Symptoms and signs, including
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
    - Significant acute renal, hepatic, or neurologic dysfunction
    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Clinical diagnosis
- Local laboratory COVID-19 test result
- Full blood count
- Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
- Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
- Number and type of any healthcare contact; duration of hospitalization and ICU stay
- Death

- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1.).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant and the study site staff will be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

established. The participant may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant to report whether or not he or she has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant to ascertain why and also to obtain details of any missed events.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will be analyzed by all-available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

Stage 3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Stage 3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for individual prophylactic BNT162 vaccines against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for individual prophylactic BNT162 vaccines against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either VE_1 >30% or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

9.2. Sample Size Determination

The study sample size for the first 2 stages of the study is not based on any statistical hypothesis testing. Stage 1 will comprise 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; up to 28 potential groups are foreseen; if all groups are fully enrolled, assuming 2 dose levels are selected following the initial dose escalation, this corresponds to a total of 420 participants. Stage 2 will include 1 or more vaccine groups selected from Stage 1, and 225 participants will be randomized per selected vaccine candidate in a 4:1 ratio to receive active vaccine (180 participants) or placebo (45 participants).

For Stage 3, with assumptions of a true VE of 60% after the last dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 11,714 evaluable participants per group or 14,643 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 29,286, based on the assumption of a 1.0% illness rate per year in the placebo group, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Stage 3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the number of candidate vaccines evaluated, the true underlying VE, and a potential early stop for efficacy or futility.

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	All eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result 21 days after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other major protocol deviations as determined by the clinician.

This document can only be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Population	Description
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other major protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window, have the efficacy measurement after the last dose of study intervention, and have no other major protocol deviations as determined by the clinician. A major protocol deviation will exclude a participant from the evaluable efficacy population from the date that it occurs through the participant's remaining follow-up.
All-available efficacy	All eligible randomized participants who receive at least 1 vaccination and have the efficacy measurement at any time after Dose 1.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.3.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody and anti-RBD binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody and anti-RBD binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

Endpoint	Statistical Analysis Methods
	virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody and anti-RBD binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 serum neutralizing titer to SARS-CoV-2 anti-S1 binding antibody and SARS-CoV-2 anti-RBD binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody/SARS-CoV-2 anti-RBD binding antibody at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 serum neutralizing titers minus SARS-CoV-2 anti-S1 binding antibody for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with antibody levels ≥ predefined threshold(s) in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody levels and/or anti-RBD binding antibody levels, percentages (and 2-sided 95% CIs) of participants with antibody levels ≥ predefined thresholds will be provided for each investigational product within each group at each of the following time points: • Stage 3 cohort(s): 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination The Clopper-Pearson method will be used to calculate the CIs. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity	For Stage 3 participants with and without confirmed COVID-19, severe COVID-19, or SARS-CoV-2 infection without confirmed COVID-19: **GMTs/GMCs of SARS-CoV-2 serum neutralizing titers, SARS-CoV-2 anti-S1 binding antibody and anti-RBD binding antibody, and SARS-CoV-2 NVA-specific binding antibody**

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Endpoint	Statistical Analysis Methods
	For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at 1, 6, 12, and 24 months after completion of vaccination. Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 serum neutralizing titers, SARS-CoV-2 anti-S1 binding antibody and anti-RBD binding antibody, and SARS-CoV-2 NVA-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at 1, 6, 12, and 24 months after completion of vaccination. GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with antibody levels ≥ predefined threshold(s) for SARS-CoV-2 serological parameters at baseline** For SARS-CoV-2 serum neutralizing titers, SARS-CoV-2 anti-S1 binding antibody levels and/or anti-RBD binding antibody levels, SARS-CoV-2 NVA-specific binding antibody, and SARS-CoV-2 detection by NAAT, percentages (and 2-sided 95% CIs) of participants with antibody levels ≥ predefined threshold(s) will be provided for each investigational product within each group at baseline and 1, 6, 12, and 24 months after completion of vaccination. The Clopper-Pearson method will be used to calculate the CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Endpoint	Statistical Analysis Methods
	For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 serum neutralizing titers, SARS-CoV-2 S1-specific binding antibody, and RBD-specific binding antibody after Dose 1 and after Dose 2.

9.4.2. Efficacy Analyses

The statistical analysis of efficacy will be based on the evaluable efficacy population (primary analysis) and the all-available efficacy population as defined in Section 9.3.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group 7 days after the last dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in participants with and without evidence of infection before vaccination for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Endpoint	Statistical Analysis Methods
	placebo group after 7 days after the last dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values; details will be provided in the SAP.
Secondary	**Ratio of confirmed severe COVID-19 illness per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** **Ratio of confirmed severe COVID-19 illness per 1000 person-years of follow-up for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the secondary efficacy endpoints, with the same alpha-adjusted CI. The following secondary efficacy endpoints will be evaluated descriptively. **Ratio of confirmed COVID-19 illness (according to the CDC-defined symptoms) per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** **Ratio of confirmed COVID-19 illness (according to the CDC-defined symptoms) per 1000 person-years of follow-up in participants with and without evidence of infection before vaccination for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms after 7 days after the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Endpoint	Statistical Analysis Methods
	last dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[9] Missing efficacy data will not be imputed.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. For Stage 1 sentinel cohorts, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Endpoint	Statistical Analysis Methods
	Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after last dose will be provided for each vaccine group. The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory	N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 serum neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the SARS-CoV-2 S1-specific binding antibody level at the postvaccination time point to the corresponding antibody level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the SARS-CoV-2 RBD-specific binding antibody level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

9.5. Interim Analyses

As this is a sponsor open-label study during Stages 1 and 2, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Stage 3, 4 IAs are planned and will be performed by an unblinded statistical team after accrual of 32, 62, 92, and 120 cases. At each IA:

- VE for both primary objectives will be evaluated sequentially. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be done for the first primary endpoint only and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1-VE)/(2-VE)$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 6 illustrates the boundary for efficacy and futility if IAs are performed after accrual of 32 62, 92, and 120 cases in participants without evidence of infection before vaccination.

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	81.5% (5:27)	11.8% (15:17)
IA2	62	70.8% (14:48)	27.8% (26:36)
IA3	92	62.7% (25:67)	35.7% (36:57)
IA4	120	57.1% (36:84)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.9975; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤5)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤14)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥36)	Probability of Success (Cases Vaccine Group ≤36)
30	0.002	0.315	0.002	0.231	0.003	0.217	0.005
50	0.022	0.044	0.034	0.027	0.089	0.033	0.138
60	0.072	0.021	0.132	0.011	0.263	0.010	0.253
70	0.219	0.020	0.335	0.010	0.325	<0.001	0.117
80	0.553	<0.001	0.370	<0.001	0.077	<0.001	<0.001

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.008	0.020
50	0.196	0.479
60	0.204	0.924
70	0.004	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the last dose of investigational product onwards.

After the primary objectives are met, the secondary VE endpoints (confirmed severe COVID-19 in participants without evidence of infection before vaccination and confirmed severe COVID-19 in all participants) will be evaluated sequentially, by the same method used for the primary VE endpoint evaluation. Success thresholds for secondary VE will be appropriately chosen to control overall Type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Stage 1.
- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Stage 2.
- Safety data through 7 days after Dose 2 and immunogenicity data through 21 days after Dose 1 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo) in Stage 3 for a vaccine candidate/dose level that progresses directly to Stage 3.
- Safety and immunogenicity data through 1 month after Dose 2 from the first 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Stage 3.
- IAs for efficacy at 32, 62, 92, and 120 cases and futility at 32, 62, and 92 cases.
- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3.
- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available at the end of the study.

All analyses conducted on Stage 3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met
- Review of safety and/or immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate(s)/dose level(s) and schedule(s) to proceed into Stage 2. Data supporting the selection, including results for both binding antibody levels and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

serum neutralizing titers, and the ratio between them, will also be submitted to the FDA for review

- Select vaccine candidate(s)/dose level(s) and schedule(s) to proceed into Stage 3. Data supporting the selection, including results for both binding antibody levels and serum neutralizing titers, and the ratio between them, will also be submitted to the FDA for review

- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Stages 1 and 2

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Stages 1 and 2
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

If a NAAT-confirmed case in Stage 3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by 3 medically qualified Pfizer staff members to assess whether the criterion is met; the majority opinion will prevail.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. • Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccines SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccines SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccines SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccines SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccines SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccines SAE Report Form
• Facsimile transmission of the Vaccines SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccines SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccines SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use application
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support a marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Abbreviation	Term
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N/A	not applicable
NAAT	nucleic acid amplification test
non-S	nonspike protein
NVA	nonvaccine antigen
P2 S	SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Abbreviation	Term
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

At the time of the IAs at 32, 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed. If there are more severe cases in the vaccine group than in the placebo group, the DMC will be advised to recommend that enrollment be stopped if the probability of the adverse split being observed is <1%, assuming that severe cases are truly evenly split (stopping rule, see Section 8.2.3). If the probability is ≥1% and <11%, the DMC will be advised to request probability to be recalculated as each additional severe case is accrued (alert rule). This is illustrated for severe cases, from 2 to 20, in Table 10.

In Stage 3, the unblinded statistical team, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 8.2.4).

Table 10. For 2 to 20 Cases of Severe COVID-19, Probability of Observing This Number or More of Severe Cases in the Vaccine Group at a Range of True Adverse Ratios From 1:1 to 4:1

	Severe Cases Split		Probability of Observing X Severe Cases in Vaccine Group if Truly Evenly Split; STOPPING RULE: <1%	Probability of Observing X or More Severe Cases in Vaccine Group if Truly Evenly Split; ALERT RULE: <11%	Probability of Observing X or More Severe Cases in Vaccine Group With Different True Split Ratios		
Total severe cases	Vaccine (X)	Placebo	True Split Ratio (Active:Placebo)		True Split Ratio (Active:Placebo)		
True ratio			(1:1)	(1:1)	(2:1)	(3:1)	(4:1)
2	2	0					
3	3	0					
4	4	0	>1%	6.25%	19.79%	31.64%	40.96%
5	5	0	>1%	3.13%	13.20%	23.73%	32.77%
6	5	1	>1%	10.94%	35.18%	53.39%	65.54%
6	6	0	>1%	1.56%	8.81%	17.80%	26.21%
7	6	1	>1%	6.25%	26.40%	44.49%	57.67%
7	7	0	0.78%	0.78%	5.87%	13.35%	20.97%
8	7	1	>1%	3.52%	19.56%	36.71%	50.33%
8	8	0	0.39%	0.39%	3.92%	10.01%	16.78%
9	7	2	>1%	8.98%	37.80%	60.07%	73.82%
9	8	1	>1%	1.95%	14.35%	30.03%	43.62%
9	9	0	0.20%	0.20%	2.61%	7.51%	13.42%
10	8	2	>1%	5.47%	29.99%	52.56%	67.78%

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extension or variations thereof

Table 10. For 2 to 20 Cases of Severe COVID-19, Probability of Observing This Number or More of Severe Cases in the Vaccine Group at a Range of True Adverse Ratios From 1:1 to 4:1

	Severe Cases Split		Probability of Observing X Severe Cases in Vaccine Group if Truly Evenly Split; STOPPING RULE: <1%	Probability of Observing X or More Severe Cases in Vaccine Group if Truly Evenly Split; ALERT RULE: <11%	Probability of Observing X or More Severe Cases in Vaccine Group With Different True Split Ratios		
Total severe cases	Vaccine (X)	Placebo	True Split Ratio (Active:Placebo)		True Split Ratio (Active:Placebo)		
True ratio			(1:1)	(1:1)	(2:1)	(3:1)	(4:1)
10	9	1	0.98%	1.07%	10.44%	24.40%	37.58%
11	9	2	>1%	3.27%	23.48%	45.52%	61.74%
11	10	1	0.54%	0.59%	7.55%	19.71%	32.21%
12	9	3	>1%	7.30%	39.40%	64.88%	79.46%
12	10	2	>1%	1.93%	18.18%	39.07%	55.83%
12	11	1	0.29%	0.32%	5.42%	15.84%	27.49%
13	10	3	>1%	4.61%	32.33%	58.43%	74.73%
13	11	2	0.95%	1.12%	13.93%	33.26%	50.17%
14	10	4	>1%	8.98%	47.66%	74.15%	87.02%
14	11	3	>1%	2.87%	26.21%	52.13%	69.82%
14	12	2	0.56%	0.65%	10.58%	28.11%	44.81%
15	11	4	>1%	5.92%	40.51%	68.65%	83.58%
15	12	3	>1%	1.76%	21.00%	46.13%	64.82%
15	13	2	0.32%	0.37%	7.97%	23.61%	39.80%
16	11	5	>1%	10.51%	54.81%	81.03%	91.83%
16	12	4	>1%	3.84%	34.02%	63.02%	79.82%
16	13	3	0.85%	1.06%	16.66%	40.50%	59.81%
17	12	5	>1%	7.17%	47.88%	76.53%	89.43%
17	13	4	>1%	2.45%	28.24%	57.39%	75.82%
17	14	3	0.52%	0.64%	13.10%	35.30%	54.89%
18	13	5	>1%	4.81%	41.34%	71.75%	86.71%
18	14	4	>1%	1.54%	23.20%	51.87%	71.64%
18	15	3	0.31%	0.38%	10.22%	30.57%	50.10%
19	13	6	>1%	8.35%	54.43%	82.51%	93.24%
19	14	5	>1%	3.18%	35.30%	66.78%	83.69%
19	15	4	0.74%	0.96%	18.88%	46.54%	67.33%
20	14	6	>1%	5.77%	48.06%	78.58%	91.33%
20	15	5	>1%	2.07%	29.83%	61.72%	80.42%
20	16	4	0.46%	0.59%	15.22%	41.48%	62.96%

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.

4 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

5 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

6 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

7 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine. 2019;37(25):3326-34.

8 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

9 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

10 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 4, clean copy, 30 June 2020
Document Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY ADULTS

Signed By:	Date(GMT)	Signing Capacity
PPD	01-Jul-2020 10:56:00	Business Line Approver
PPD	01-Jul-2020 13:44:06	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1941f5ede\Approved\Approved On: 01-Jul-2020 13:44 (GMT)

A PHASE 1/2, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO DESCRIBE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND POTENTIAL EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY ADULTS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	N/A
Protocol Number:	C4591001
Phase:	1/2

Short Title: A Phase 1/2 Study to Describe the Safety, Tolerability, Immunogenicity, and Potential Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these candidates have been removed from the protocol. • To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

		• Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD. • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

		• Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial • Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

TABLE OF CONTENTS

LIST OF TABLES 10
1. PROTOCOL SUMMARY 12
1.1. Synopsis 12
1.2. Schema 17
1.3. Schedule of Activities 18
1.3.1. Stage 1 Sentinel Cohorts 18
1.3.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts 23
1.3.3. Stage 3 Cohort(s) 26
2. INTRODUCTION 28
2.1. Study Rationale 28
2.2. Background 28
2.2.1. Clinical Overview 29
2.3. Benefit/Risk Assessment 29
2.3.1. Risk Assessment 30
2.3.2. Benefit Assessment 31
2.3.3. Overall Benefit/Risk Conclusion 31
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 31
4. STUDY DESIGN 33
4.1. Overall Design 33
4.1.1. Stage 1 34
4.1.2. Stage 2 35
4.1.3. Stage 3 35
4.2. Scientific Rationale for Study Design 35
4.3. Justification for Dose 36
4.4. End of Study Definition 36
5. STUDY POPULATION 37
5.1. Inclusion Criteria 37
5.2. Exclusion Criteria 38
5.3. Lifestyle Considerations 40

5.3.1. Contraception....40
5.4. Screen Failures....40
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration....41
6. STUDY INTERVENTION....41
6.1. Study Intervention(s) Administered....44
6.1.1. Administration....44
6.2. Preparation/Handling/Storage/Accountability....45
6.2.1. Preparation and Dispensing....46
6.3. Measures to Minimize Bias: Randomization and Blinding....46
6.3.1. Allocation to Study Intervention....46
6.3.2. Blinding of Site Personnel....46
6.3.3. Blinding of the Sponsor....47
6.3.4. Breaking the Blind....47
6.4. Study Intervention Compliance....47
6.5. Concomitant Therapy....47
6.5.1. Prohibited During the Study....48
6.5.2. Permitted During the Study....48
6.6. Dose Modification....49
6.7. Intervention After the End of the Study....49
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL....49
7.1. Discontinuation of Study Intervention....49
7.2. Participant Discontinuation/Withdrawal From the Study....49
7.2.1. Withdrawal of Consent....50
7.3. Lost to Follow-up....50
8. STUDY ASSESSMENTS AND PROCEDURES....51
8.1. Efficacy and/or Immunogenicity Assessments....52
8.1.1. Biological Samples....53
8.2. Safety Assessments....54
8.2.1. Clinical Safety Laboratory Assessments (Sentinel-Cohort Participants Only)....54

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

8.2.2. Electronic Diary 55
8.2.2.1. Grading Scales 55
8.2.2.2. Local Reactions 55
8.2.2.3. Systemic Events 56
8.2.2.4. Fever 57
8.2.2.5. Antipyretic Medication 58
8.2.3. Stopping Rules 58
8.2.3.1. Randomization and Vaccination After a Stopping Rule Is Met 59
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 Disease 59
8.2.5. Pregnancy Testing 60
8.3. Adverse Events and Serious Adverse Events 60
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 60
8.3.1.1. Reporting SAEs to Pfizer Safety 61
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 61
8.3.2. Method of Detecting AEs and SAEs 61
8.3.3. Follow-up of AEs and SAEs 62
8.3.4. Regulatory Reporting Requirements for SAEs 62
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 62
8.3.5.1. Exposure During Pregnancy 63
8.3.5.2. Exposure During Breastfeeding 64
8.3.5.3. Occupational Exposure 65
8.3.6. Medication Errors 65
8.4. Treatment of Overdose 66
8.5. Pharmacokinetics 66
8.6. Pharmacodynamics 66
8.7. Genetics 67
8.8. Biomarkers 67
8.9. Immunogenicity Assessments 67
8.10. Health Economics 67

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

8.11. Study Procedures 67
8.11.1. Stage 1 Sentinel Cohorts 67
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 67
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 68
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 71
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 72
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 73
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 75
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 76
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 77
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 4) 78
8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4) 79
8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4) 79
8.11.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts 79
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 79
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1) 82
8.11.2.3. Visit 3 – 2-Week Follow-up Visit: (12 to 16 Days After Visit 2) 84
8.11.2.4. Visit 4 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 2) 84
8.11.2.5. Visit 5 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 2) 85
8.11.2.6. Visit 6 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2) 85
8.11.2.7. Visit 7 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2) 86
8.11.3. Stage 3 Cohort(s) 86

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

8.11.3.1. Visit 1 – Vaccination 1: (Day 1) 86
8.11.3.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)....89
8.11.3.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)....90
8.11.3.4. Visit 4 – 6-Month Safety Telephone Contact: (154 to 168 Days After Visit 2) 91
8.11.3.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)....92
8.11.3.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)....92
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 92
8.13. COVID-19 Disease Surveillance (All Participants)....94
8.13.1. Potential COVID-19 Illness Telehealth Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)....94
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)....95
8.14. Communication and Use of Technology....96
9. STATISTICAL CONSIDERATIONS....96
9.1. Estimands and Statistical Hypotheses....96
9.1.1. Estimands....96
9.1.2. Statistical Hypotheses....97
9.2. Sample Size Determination....97
9.3. Analysis Sets....98
9.4. Statistical Analyses....99
9.4.1. Immunogenicity Analyses....99
9.4.2. Efficacy Analyses....102
9.4.3. Safety Analyses....103
9.4.4. Other Analyses....104
9.5. Interim Analyses....105
9.5.1. Analysis Timing....105
9.6. Data Monitoring Committee or Other Independent Oversight Committee....105
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS....107

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 107
10.1.1. Regulatory and Ethical Considerations 107
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP.....107
10.1.2. Informed Consent Process 108
10.1.3. Data Protection 109
10.1.4. Dissemination of Clinical Study Data 109
10.1.5. Data Quality Assurance 110
10.1.6. Source Documents 112
10.1.7. Study and Site Start and Closure 112
10.1.8. Sponsor's Qualified Medical Personnel 113
10.2. Appendix 2: Clinical Laboratory Tests 114
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 116
10.3.1. Definition of AE 116
10.3.2. Definition of SAE 117
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs.....119
10.3.4. Reporting of SAEs.....122
10.4. Appendix 4: Contraceptive Guidance 123
10.4.1. Male Participant Reproductive Inclusion Criteria 123
10.4.2. Female Participant Reproductive Inclusion Criteria.....123
10.4.3. Woman of Childbearing Potential 124
10.4.4. Contraception Methods.....125
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 127
10.6. Appendix 6: Abbreviations 129
11. REFERENCES 132

LIST OF TABLES

Table 1. Potential Groups in Stage 1 42
Table 2. Local Reaction Grading Scale 56
Table 3. Systemic Event Grading Scale.....57
Table 4. Scale for Fever.....58

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 98
Table 6. Laboratory Abnormality Grading Scale 114

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2 Study to Describe the Safety, Tolerability, Immunogenicity, and Potential Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no vaccines to prevent infection with SARS-CoV-2 or antiviral drugs to treat COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein (P2 S) (version 9), or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that may be tested in this study are therefore:

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and potential efficacy of these 2 prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

It is expected that the various candidate vaccines may not all be available from the start of the study, in which case they will be rolled into the study in a consecutive fashion as they are released. A Phase 1/2 study of the same vaccine candidates (BNT162-01), conducted in Germany by BioNTech in adults 18 to 55 years of age, is planned to start in April 2020. Study C4591001 is designed to complement and expand upon the German study and confirm the optimal vaccine candidate(s), dose level(s), number of doses, and schedule of administration.

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, in sentinel cohorts from Stage 1, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: ***Stage 1 Sentinel Cohorts:*** 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts:*** 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 3 Cohort(s):*** 1, 12, and 24 months after Dose 2	

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 serum neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 S1-specific binding antibody levels and RBD-specific binding antibody levels
To evaluate the efficacy of prophylactic BNT162 vaccines against confirmed COVID-19	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 serum neutralizing titers to the geometric mean of SARS-CoV-2–specific binding antibody levels at each time point In participants complying with the key protocol criteria (evaluable participants) following receipt of the last dose of study intervention: 100 × (1 – illness rate ratio) [ratio of active vaccine to placebo]	• SARS-CoV-2 serum neutralizing titers • SARS-CoV-2 S1-specific binding antibody levels • SARS-CoV-2 RBD-specific binding antibody levels COVID-19 incidence per 1000 person-years of follow-up
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
To describe the relationship between SARS-CoV-2 serological parameters and: • NAAT-confirmed COVID-19 • Symptomatic SARS-CoV-2 infection • Asymptomatic SARS-CoV-2 infection		Nonvaccine antigen SARS-CoV-2 antibody levels

Overall Design

This is a Phase 1/2, randomized, placebo-controlled, observer-blind, dose-finding, and vaccine candidate–selection study in healthy adults.

The study will evaluate the safety, tolerability, immunogenicity, and potential efficacy of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19:

- As a 2-dose (separated by 21 or 60 days) or single-dose schedule
- At various different dose levels

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema europa eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- In 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age])

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study consists of 3 stages. Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3: a final candidate/dose large-scale stage. These stages, and the progression between them, are detailed in the schema (Section 1.2).

Number of Participants

Each group in Stage 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this stage, assuming 2 dose levels are selected following the initial dose escalation, up to 28 potential groups are foreseen; if all groups are fully enrolled, this corresponds to a total of 420 participants.

Each group in Stage 2 will comprise 225 participants (180 receiving active vaccine and 45 receiving placebo). The total number of participants to be enrolled in this stage depends on the number of groups to be pursued.

The vaccine candidate/dose level selected for Stage 3 will comprise 3000 participants. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study may evaluate single-dose and 2-dose (separated by 21 or 60 days) schedules of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 50 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg, 50 µg, 100 µg

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Stage 1 and Stage 2 dosing arms that are not evaluated in Stage 3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The study sample size for the first 2 stages of the study is not based on any statistical hypothesis testing. For the third stage, with assumptions of a true vaccine efficacy (VE) of 70%, 53 cases of COVID-19 will provide 90% power to conclude true VE >20%. This would be achieved with 3000 participants per group, based on the assumption of a 1.7% incidence rate in the placebo group, and 20% of the participants being nonevaluable.

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, abnormal hematology and chemistry laboratory parameters (sentinel cohorts only), and AEs and SAEs, for each vaccine group. A 3-tier approach will be used to summarize AEs.

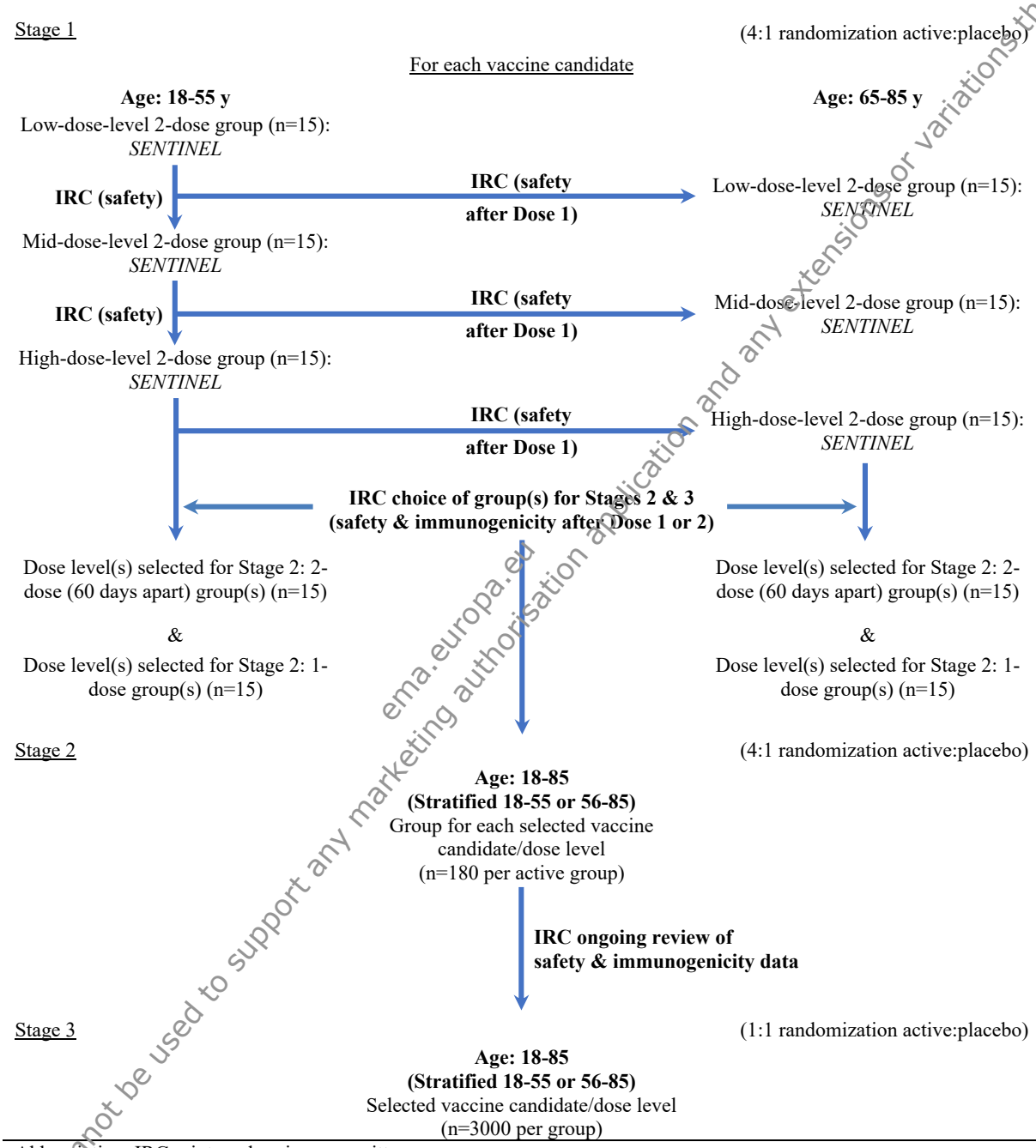
The secondary immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 serum neutralizing titers, SARS-CoV-2 S1-specific binding antibody levels, and RBD-specific binding antibody levels at the various time points.

For the secondary efficacy objective, VE is defined as VE = 100 × (1 – IRR), where IRR is the illness rate ratio, the calculated ratio of COVID-19 incidence in the active vaccine group to the incidence in the placebo group. The null hypothesis (VE ≤ 20%) will be rejected if the lower bound of the 95% CI for VE is >20%; no interim analysis of VE is planned.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

1.2. Schema



Abbreviation: IRC = internal review committee.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Stage 1 Sentinel Cohorts

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						

This document cannot be used to support any marketing authorisation application. ema.europa.eu and any extensions or variations thereof

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[a]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[b]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[d] ~170 mL	~50 mL + optional[d] ~170 mL	~50 mL + optional[d] ~170 mL	~50 mL	~50 mL	~50 mL		~50 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[c]		X			X								
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X											
Provide thermometer and measuring device		X			X								

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►	◄	►							
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collect e-diary or assist the participant to delete application											X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
b. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
c. The first 5 participants in in each sentinel group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
d. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 7 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	1	2	3	4	5	6	7	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**12 to 16 Days After Visit 2**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X								
Assign participant number	X								
Obtain demography and medical history data	X								
Perform physical examination	X								
Measure vital signs	X								
Perform urine pregnancy test (if appropriate)	X	X							
Collect nonstudy vaccine information	X	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X	X
Confirm eligibility	X	X							
Measure temperature (body)	X	X							
Review temporary delay criteria	X	X							
Confirm use of contraceptives (if appropriate)	X	X	X	X					

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Visit Number	1	2	3	4	5	6	7	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**12 to 16 Days After Visit 2**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain randomization number and study intervention allocation	X								
Collect blood sample for immunogenicity assessment	~25 mL	~25 mL	~25 mL	~25 mL	~25 mL	~25 mL	~25 mL		~50 mL
Obtain nasal (midturbinate) swab	X	X						X	
Administer study intervention	X	X							
Assess acute reactions for at least 30 minutes after study intervention administration	X	X							
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X								
Provide participant with thermometer and measuring device	X	X							
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	◄——►	◄——►							
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X	X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	7	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**12 to 16 Days After Visit 2**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collect e-diary or assist the participant to delete application							X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)								X	X

Abbreviation: e-diary = electronic diary.

a. The window for Visit 2 is dependent on the dosing schedule for the assigned group.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Stage 3 Cohort(s)

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	1	2	3	4	5	6	Unplanned 1	Unplanned 2
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Safety Telephone Contact**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform physical examination	X							
Measure vital signs	X							
Perform urine pregnancy test (if appropriate)	X	X						
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Measure temperature (body)	X	X						
Review temporary delay criteria	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Obtain randomization number and study intervention allocation	X							
Collect blood sample for immunogenicity assessment	~25 mL		~25 mL		~25 mL	~25 mL		~50 mL
Obtain nasal (midturbinate) swab	X	X					X	

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Safety Telephone Contact**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Administer study intervention	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide participant with thermometer and measuring device	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	◄——►	◄——►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application						X		
Telephone contact				X				
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviation: e-diary = electronic diary.

a. The window for Visit 2 is dependent on the dosing schedule(s) selected for the Stage 3.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy adults.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, immunogenicity, and potential efficacy of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19 in healthy adults. There are currently no vaccines to prevent infection with SARS-CoV-2 or antiviral drugs to treat COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Two SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein (P2 S) (version 9), or a trimerized SARS-CoV-2 spike glycoprotein-receptor binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that may be tested in this study are therefore:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding P2 S.

2.2.1. Clinical Overview

BNT162 vaccines have not been administered to humans before and thus there are no previous clinical data with these specific vaccines. However, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines are expected to have a favorable safety profile with mild, localized, and transient effects.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there are currently no data available from clinical trials on the use of BNT162 vaccines in humans, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, support a favorable risk/benefit profile. Anticipated AEs after vaccination are expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates support initiation of this Phase 1/2 clinical study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the investigator's brochure (IB), which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The study design includes the use of sentinel cohorts and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place for sentinel cohorts. The first 5 sentinel-cohort participants in each group will be observed for 4 hours after vaccination to assess any immediate AEs.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The study design includes the use of sentinel cohorts and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC and DMC will also review safety data throughout the study. Stopping rules are also in place for sentinel cohorts. The first 5 sentinel-cohort participants in each group will be observed for 4 hours after vaccination to assess any immediate AEs.
Potential for COVID-19 disease enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	The study excludes participants with likely previous or current COVID-19. All participants are followed for SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 serum neutralizing titers, and COVID-19 illness, including markers of severity.
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of a potentially efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic and antibody testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, in sentinel cohorts from Stage 1, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: ***Stage 1 Sentinel Cohorts:*** 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts:*** 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 3 Cohort(s):*** 1, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 serum neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 S1-specific binding antibody levels and RBD-specific binding antibody levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 serum neutralizing titers to the geometric mean of SARS-CoV-2–specific binding antibody levels at each time point	• SARS-CoV-2 serum neutralizing titers • SARS-CoV-2 S1-specific binding antibody levels • SARS-CoV-2 RBD-specific binding antibody levels
To evaluate the efficacy of prophylactic BNT162 vaccines against confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants) following receipt of the last dose of study intervention: 100 × (1 – illness rate ratio) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Objectives	Estimands	Endpoints
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
To describe the relationship between SARS-CoV-2 serological parameters and: • NAAT-confirmed COVID-19 • Symptomatic SARS-CoV-2 infection • Asymptomatic SARS-CoV-2 infection		Nonvaccine antigen SARS-CoV-2 antibody levels

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1/2, randomized, placebo-controlled, observer-blind, dose-finding, and vaccine candidate–selection study in healthy adults.

The study will evaluate the safety, tolerability, immunogenicity, and potential efficacy of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19:

- As a 2-dose (separated by 21 or 60 days) or single-dose schedule
- At various different dose levels
- In 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age])

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study consists of 3 stages. Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3; a final candidate/dose large-scale stage. These stages, and the progression between them, are detailed in the schema (Section 1.2).

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Stage 1 and Stage 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

4.1.1. Stage 1

Each group (vaccine candidate/dose level/age group/number of doses) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo. On Day 22, those in 2-dose groups will receive the same vaccine they received on Day 1; for those in single-dose groups, all will receive placebo. Full details of all potential groups in Stage 1 may be found in Table 1.

For each vaccine candidate/dose level/age group, the 15 participants randomized into each 2-dose group will comprise a sentinel cohort, to which the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment:
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

Once the IRC has selected a vaccine candidate/dose level to proceed into Stage 2, for each age cohort, 2 additional groups will be enrolled into Stage 1 for that vaccine candidate/dose level:

- A 2-dose group, with the 2 doses administered 60 days apart rather than 21

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- A 1-dose group

In this stage, assuming 2 dose levels are selected following the initial dose escalation, up to 28 potential groups are foreseen; if all groups are fully enrolled, this corresponds to a total of 420 participants.

4.1.2. Stage 2

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 or more groups (vaccine candidate/dose level) may be selected to proceed into Stage 2. Participants in this stage will be 18 to 85 years of age, stratified equally: 18 to 55 or 56 to 85 years. Commencement of each age stratum will be dependent upon satisfactory safety and immunogenicity data from the 18- to 55-year and 65- to 85-year groups from Stage 1, respectively. It is therefore possible that the 2 age strata may not start concurrently.

In each group selected for Stage 2, it is intended that 225 participants will be randomized in a 4:1 ratio to receive active vaccine (180 participants) or placebo (45 participants).

4.1.3. Stage 3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 group may be selected to proceed into Stage 3. Participants in this stage will be 18 to 85 years of age, stratified equally: 18 to 55 years or 56 to 85 years. As in Stage 2, it is possible that the 2 age strata may not start concurrently.

The vaccine candidate/dose level selected for Stage 3 will comprise 3000 participants. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Stage 1 and Stage 2 dosing arms that are not evaluated in Stage 3.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences respiratory symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data are not currently available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Taken together, the planned starting doses in this study in healthy participants are considered to be safe, but still sufficient to induce an antiviral immune response.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Stages 1 and 2 in groups that do not proceed to Stage 3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, 65 and 85 years, inclusive, or 18 and 85 years, inclusive, at randomization (dependent upon study stage).

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.

Informed Consent:

4. Capable of giving personal signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. **Stages 1 and 2 only:** Previous clinical or microbiological diagnosis of COVID-19.

6. **Sentinel participants in Stage 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - Chronic liver disease
    - Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
    - Resident in a long-term facility
    - BMI >30 kg/m^2
    - Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Sentinel participants in Stage 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for sentinel participants in Stage 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Sentinel participants in Stage 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Sentinel participants in Stage 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.au

19. **Sentinel participants in Stage 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Sentinel participants in Stage 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Sentinel participants in Stage 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
   - New or increased cough;
   - New or increased shortness of breath;
   - New or increased sore throat;
   - New or increased wheezing;
   - New or increased sputum production;
   - New or increased nasal congestion;
   - New or increased nasal discharge;
   - Loss of taste/smell.
2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.
3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.
4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study may evaluate 2-dose (separated by 21 or 60 days) and single-dose schedules of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age]).

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

These 2 investigational RNA vaccine candidates, with the addition of saline placebo, are the 3 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 50 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg, 50 µg, 100 µg
- Normal saline (0.9% sodium chloride solution for injection)

A list of all potential groups in the Stage 1 are shown in Table 1. Each of these groups may or may not progress to the later stages of the study.

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
2-Dose Groups (Sentinel Cohorts)			**Day 1**			**Day 22**		
b1-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	10 µg	(n=12) (n=3)	BNT162b1 Placebo	10 µg	(n=12) (n=3)
b1-20-2-Y (Sentinel) [modRNA 20 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	20 µg	(n=12) (n=3)	BNT162b1 Placebo	20 µg	(n=12) (n=3)
b1-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	30 µg	(n=12) (n=3)	BNT162b1 Placebo	30 µg	(n=12) (n=3)
b1-50-2-Y (Sentinel) [modRNA 50 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	50 µg	(n=12) (n=3)	BNT162b1 Placebo	50 µg	(n=12) (n=3)
b1-100-2-Y (Sentinel) [modRNA 100 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	100 µg	(n=12) (n=3)	BNT162b1 Placebo	100 µg	(n=12) (n=3)
b2-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	10 µg	(n=12) (n=3)	BNT162b2 Placebo	10 µg	(n=12) (n=3)
b2-20-2-Y (Sentinel) [modRNA 20 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	20 µg	(n=12) (n=3)	BNT162b2 Placebo	20 µg	(n=12) (n=3)
b2-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	30 µg	(n=12) (n=3)	BNT162b2 Placebo	30 µg	(n=12) (n=3)
b2-50-2-Y (Sentinel) [modRNA 50 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	50 µg	(n=12) (n=3)	BNT162b2 Placebo	50 µg	(n=12) (n=3)
b2-100-2-Y (Sentinel) [modRNA 100 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	100 µg	(n=12) (n=3)	BNT162b2 Placebo	100 µg	(n=12) (n=3)
b1-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	10 µg	(n=12) (n=3)	BNT162b1 Placebo	10 µg	(n=12) (n=3)
b1-20-2-O (Sentinel) [modRNA 20 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	20 µg	(n=12) (n=3)	BNT162b1 Placebo	20 µg	(n=12) (n=3)
b1-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	30 µg	(n=12) (n=3)	BNT162b1 Placebo	30 µg	(n=12) (n=3)
b1-50-2-O (Sentinel) [modRNA 50 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	50 µg	(n=12) (n=3)	BNT162b1 Placebo	50 µg	(n=12) (n=3)
b1-100-2-O (Sentinel)	15	65 to 85	BNT162b1 Placebo	100 µg	(n=12) (n=3)	BNT162b1 Placebo	100 µg	(n=12) (n=3)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
[modRNA 100 µg (2 doses)]								
b2-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	10 µg	(n=12) (n=3)	BNT162b2 Placebo	10 µg	(n=12) (n=3)
b2-20-2-O (Sentinel) [modRNA 20 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	20 µg	(n=12) (n=3)	BNT162b2 Placebo	20 µg	(n=12) (n=3)
b2-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	30 µg	(n=12) (n=3)	BNT162b2 Placebo	30 µg	(n=12) (n=3)
b2-50-2-O (Sentinel) [modRNA 50 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	50 µg	(n=12) (n=3)	BNT162b2 Placebo	50 µg	(n=12) (n=3)
b2-100-2-O (Sentinel) [modRNA 100 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	100 µg	(n=12) (n=3)	BNT162b2 Placebo	100 µg	(n=12) (n=3)
Single-Dose Groups			**Day 1**			**Day 22**		
b1-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b2-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b1-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b2-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
2-Dose Groups (Longer Schedule)			**Day 1**			**Day 61**		
b1-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b1 Placebo	TBD	(n=12) (n=3)	BNT162b1 Placebo	TBD	(n=12) (n=3)
b2-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b2 Placebo	TBD	(n=12) (n=3)	BNT162b2 Placebo	TBD	(n=12) (n=3)
b1-x-2L-O [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162b1 Placebo	TBD	(n=12) (n=3)	BNT162b1 Placebo	TBD	(n=12) (n=3)
b2-x-2L-O [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162b2 Placebo	TBD	(n=12) (n=3)	BNT162b2 Placebo	TBD	(n=12) (n=3)

Abbreviations: modRNA = nucleoside-modified messenger ribonucleic acid; TBD = to be determined.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline placebo
Type	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-,30-, 50-, 100-µg	10-, 20-,30-, 50-, 100-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

6.1.1. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Stage 1 sentinel-cohort participants, Visits 1 and 2 for all other participants) in accordance with the study's SoA. The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Stage 1 and in Stage 2. Sponsor staff will be blinded to study intervention allocation in Stage 3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study.

Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate). Unblinded clinician(s) who are not direct members of the study team will review unblinded protocol deviations.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Stage 1 sentinel cohorts, Visit 5 for Stage 1 nonsentinel cohorts and Stage 2 participants, and Visit 4 for Stage 3 participants).

- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- In addition, for participants enrolled in the Stage 1 sentinel cohorts, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 for Stage 1 sentinel cohorts, Visit 4 for Stage 1 nonsentinel cohorts and Stage 2 participants, and Visit 3 for Stage 3 participants).

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Stage 1 sentinel cohorts.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Inhaled (except in Stage 1 sentinel cohorts – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria).

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcomes if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 530 mL for participants in the Stage 1 sentinel cohorts; 350 mL for participants in the Stage 1 nonsentinel cohorts and Stage 2 participants; and 200 mL for Stage 3 participants. Additionally, 50 mL of blood will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Select participants in the sentinel cohorts of Stage 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 700 mL during the 24-month study period. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, a telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. Four definitions of potential SARS-CoV-2–related cases will be considered:

- Centrally confirmed COVID-19: presence of at least 1 symptom described in Section 8.13 and SARS-CoV-2 NAAT positive at central laboratory
- Locally confirmed COVID-19: presence of at least 1 symptom described in Section 8.13 and investigator-confirmed SARS-CoV-2 NAAT positive at a local testing facility
- Centrally confirmed symptomatic seroconversion to SARS-CoV-2 (exploratory): presence of at least 1 symptom described in Section 8.13 and a positive nonvaccine antigen SARS-CoV-2 antibody result in a participant whose most recent prior nonvaccine antigen SARS-CoV-2 antibody result was negative
- Centrally confirmed asymptomatic seroconversion to SARS-CoV-2 (exploratory): positive nonvaccine antigen SARS-CoV-2 antibody result in a participant with a prior nonvaccine antigen SARS-CoV-2 antibody result was negative

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 serum neutralization assay
- SARS-CoV-2 S1-specific IgG direct Luminex immunoassay
- SARS-CoV-2 RBD-specific IgG direct Luminex immunoassay
- Nonvaccine antigen (NVA) Ig direct Luminex immunoassay. The NVA will include a SARS-CoV-2 target antigen that is not derived from the S glycoprotein, most likely an antigen derived from the SARS-CoV-2 nucleoprotein.

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Stage 1 sentinel cohorts (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in the sentinel cohorts of Stage 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Stage 1 sentinel group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2.

8.2.1. Clinical Safety Laboratory Assessments (Sentinel-Cohort Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

8.2.2. Electronic Diary

Participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. The participant will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 2. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 3.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Table 3. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 4.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Table 4. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Stopping Rules

The following stopping rules are in place for all Stage 1 sentinel-cohort participants, based on review of AE data and e-diary reactogenicity data. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during the Stage 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19 disease.

8.2.3.1. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC and DMC have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 Disease

As this is a sponsor open-label study during Stages 1 and 2, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment.

Participants in all stages of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13). All NAAT-confirmed cases will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6). In addition, instances of symptomatic and asymptomatic seroconversion to SARS-CoV-2 (see Section 8.1) will be reviewed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
European Medicines Agency

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review. Since the DMC is able to review unblinded information, it will also be able to compare cases in active vaccine and placebo recipients in Stage 3 (when sponsor staff will be blinded).

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Stage 1 sentinel-cohort participants, Visit 4 for Stage 1 nonsentinel participants and Stage 2 participants, and Visit 3 for Stage 3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

SAEs will be collected from the time the participant provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Stage 1 sentinel-cohort participants, Visit 5 for Stage 1 non–sentinel-cohort participants and Stage 2 participants, and Visit 4 for Stage 3 participants).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccines SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccines SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccines SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are recorded on the CRF. AEs and SAEs that begin after obtaining informed consent but before the start of study intervention will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section. AEs and SAEs that begin after the start of study intervention are recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
eMA ema.europa.eu

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccines SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccines SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccines SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccines SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

8.3.6. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccines SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

8.11.1. Stage 1 Sentinel Cohorts

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.5.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.

- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- The first 5 participants vaccinated in each Stage 1 sentinel group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy (see Section 7.1).

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
the european
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- If the participant (select participants only, details will be provided by the Sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 100 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)

The window for Visit 2 is dependent on the dosing schedule for the assigned group.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.11.2.3. Visit 3 – 2-Week Follow-up Visit: (12 to 16 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.4. Visit 4 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.5. Visit 5 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.7. Visit 7 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.3. Stage 3 Cohort(s)

8.11.3.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

8.11.3.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)

The window for Visit 2 is dependent on the dosing schedule(s) selected for Stage 3.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.3.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.3.4. Visit 4 – 6-Month Safety Telephone Contact: (154 to 168 Days After Visit 2)

- Contact the participant by telephone in order to obtain the following information.
- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

8.11.3.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.3.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 25 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff, such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

8.13. COVID-19 Disease Surveillance (All Participants)

If a participant experiences any of the following, he or she is instructed to contact the site immediately, and if confirmed, participate in a telehealth visit as soon as possible, optimally within 3 days of symptom onset. Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- New or increased sore throat;
- New or increased wheezing;
- New or increased sputum production;
- New or increased nasal congestion;
- New or increased nasal discharge;
- Loss of taste/smell.

8.13.1. Potential COVID-19 Illness Telehealth Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This telehealth visit is expected to involve the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several telehealth contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory. The result from this swab will be provided to the site once it is available, but this will not be in real time, and cannot be relied upon to direct clinical care. Therefore, the participant should be encouraged to seek care, if appropriate, from his or her usual provider.

- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:

  - Symptoms
  - Clinical diagnosis
  - Local laboratory COVID-19 test result
  - Full blood count
  - C-reactive protein
  - Number and type of any healthcare contacts; duration of hospitalization and intensive care unit stay
  - Need for oxygen therapy
  - Need for ventilation

- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).

- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- The investigator or an authorized designee completes the CRFs.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant and the study site staff will be established. The participant may be able to utilize his or her own device to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant to report whether or not he or she has experienced symptoms that could represent a potential COVID-19 illness (see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

At the end of Stage 3, the vaccine efficacy (VE) will be evaluated. VE is defined as VE = 100 × (1 – IRR), where IRR is the illness rate ratio, the calculated ratio of the COVID-19 illness rate in the active vaccine group to the incidence rate in the placebo group. The efficacy hypothesis is:

H_0: VE ≤20% vs H_a: VE >20%

where H_0 and H_a represent null hypothesis and alternative hypothesis. For participants with multiple illnesses, only the first COVID-19 confirmed case will contribute to the VE calculation in the hypothesis test.

The efficacy will be demonstrated if the null hypothesis VE ≤20% is rejected at the 0.025 significance level, that is, when the lower limit of the 2-sided 95% CI for VE is >20%, which is derived using the Clopper-Pearson method as described by Agresti.[9]

9.2. Sample Size Determination

The study sample size for the first 2 stages of the study is not based on any statistical hypothesis testing. Stage 1 will comprise 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; up to 28 potential groups are foreseen; if all groups are fully enrolled, assuming 2 dose levels are selected following the initial dose escalation, this corresponds to a total of 420 participants. Stage 2 will include 1 or more vaccine groups selected from Stage 1, and 225 participants will be randomized per selected vaccine candidate in a 4:1 ratio to receive active vaccine (180 participants) or placebo (45 participants).

For Stage 3, for the selected vaccine candidate/dose level, with assumptions of a true vaccine efficacy (VE) of 70%, 53 cases of COVID-19 will provide 90% power to conclude true VE >20%. This would be achieved with 3000 participants per group (1:1 randomization ratio), based on the assumption of a 1.7% incidence rate in the placebo group, and 20% of the participants being nonevaluable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=3000
0.10%	0.01	0.04	0.16	0.95
0.50%	0.06	0.20	0.59	>0.99
1.00%	0.11	0.36	0.84	>0.99
2.00%	0.22	0.60	0.97	>0.99
3.00%	0.31	0.75	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	All eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result 21 days after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other major protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other major protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Population	Description
Evaluable efficacy	All eligible randomized participants who receive vaccination(s) as randomized within the predefined window, have the efficacy measurement after the last dose of study intervention, and have no other major protocol deviations as determined by the clinician.
All-available efficacy	All eligible randomized participants who receive at least 1 vaccination and have the efficacy measurement at any time after Dose 1.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific binding antibody levels and RBD-specific binding antibody levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product (active/placebo) within each group before vaccination and at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 12, and 24 months after Dose 2 Geometric means and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on the t-distribution, and then exponentiating the results. **GMFRs of SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific antibody levels and RBD-specific binding antibody levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and transformed back to the original scale. Two-sided CIs will be obtained by

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Endpoint	Statistical Analysis Methods
	calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and transforming the limits back to the original scale. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific antibody levels and RBD-specific binding antibody levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 serum neutralizing titer to SARS-CoV-2 S1-specific antibody and SARS-CoV-2 RBD-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific binding antibody levels and RBD-specific binding antibody levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 Cohort(s): 1, 12, and 24 months after Dose 2

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific antibody/SARS-CoV-2 RBD-specific binding antibody at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 serum neutralizing titers minus SARS-CoV-2 S1-specific antibody for each participant) and transformed back to the original scale. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and transforming the limits back to the original scale. The same analysis methods will be applied to the immunogenicity endpoints in Stages 2 and 3. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Tertiary/ exploratory immunogenicity	**Correlation of an RT-PCR–confirmed COVID-19 infection and seropositivity/seroconversion measured by nonvaccine antigen SARS-CoV-2 antibody** If sufficient data are collected, percentages (and 2-sided 95% CIs) of participants with confirmed COVID-19 and nonvaccine antigen SARS-CoV-2 antibody levels after Dose 1 and after Dose 2 will be provided. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 serum neutralizing titers, SARS-CoV-2 S1-specific antibody, and RBD-specific binding antibody after Dose 1 and after Dose 2.

9.4.2. Efficacy Analyses

The statistical analysis of efficacy will be based on the evaluable efficacy population (primary analysis) and the all-available efficacy population as defined in Section 9.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Endpoint	Statistical Analysis Methods
Secondary efficacy	**Ratio of COVID-19 incidence per 1000 person-years of follow-up for the active vaccine group to the placebo group** Vaccine efficacy will be estimated by 100 × (1 – IRR), where IRR is the illness rate ratio, the calculated ratio of COVID-19 infection incidence per 1000 person-years follow-up in the active vaccine group to the corresponding incidence in the placebo group after 2 doses. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. For the primary analysis, missing efficacy data will not be imputed. A sensitivity analysis may be performed by imputing missing values; details will be provided in the SAP.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	• Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. • For Stage 1 sentinel cohorts, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. • AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Endpoint	Statistical Analysis Methods
	term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. • Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. • SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after last dose will be provided for each vaccine group. • The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	• Not applicable (N/A)
Exploratory	• N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 serum neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the SARS-CoV-2 S1-specific binding antibody level at the postvaccination time point to the corresponding antibody level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the SARS-CoV-2 RBD-specific binding antibody level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

9.5. Interim Analyses

No formal interim analysis is planned in this study. As this is a sponsor open-label study during Stages 1 and 2, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 3 weeks after Dose 2 for Stage 1.
- Complete safety and immunogenicity analysis approximately 3 weeks after Dose 2 for Stage 2.
- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3.
- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available at the end of the study.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC and a DMC. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met
- Review of safety and/or immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate(s)/dose level(s) and schedule(s) to proceed into Stage 2. Data supporting the selection, including results for both binding antibody levels and serum neutralizing titers, and the ratio between them, will also be submitted to the FDA for review

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Select vaccine candidate(s)/dose level(s) and schedule(s) to proceed into Stage 3. Data supporting the selection, including results for both binding antibody levels and serum neutralizing titers, and the ratio between them, will also be submitted to the FDA for review

- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 6).

Table 6. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500

This document can be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Table 6. Laboratory Abnormality Grading Scale

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
Chemistry	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccines SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccines SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccines SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and EDP supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccines SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccines SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccines SAE Report Form
• Facsimile transmission of the Vaccines SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccines SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccines SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use application
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Abbreviation	Term
HBc Ab	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
modRNA	nucleoside-modified messenger ribonucleic acid
N/A	not applicable
NAAT	nucleic acid amplification test
NVA	nonvaccine antigen
P2 S	SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein

This document cannot be used to support any marketing authorization application and any extensions or variations thereof

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Abbreviation	Term
PCR	polymerase chain reaction
PI	principal investigator
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
This document is purchased by eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): therapeutic options. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Accessed: 12 Apr 2020.

4 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

5 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

6 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

7 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine. 2019;37(25):3326-34.

8 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

9 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

10 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 3 Clean Copy, 10 June 2020
Document Title:	A PHASE 1/2, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO DESCRIBE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND POTENTIAL EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY ADULTS

Signed By:	Date(GMT)	Signing Capacity
PPD	11-Jun-2020 13:50:23	Business Line Approver
PPD	11-Jun-2020 13:54:01	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193b65c72\Approved\Approved On: 11-Jun-2020 13:54 (GMT)

A PHASE 1/2, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO DESCRIBE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND POTENTIAL EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY ADULTS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	N/A
Protocol Number:	C4591001
Phase:	1/2

Short Title: A Phase 1/2 Study to Describe the Safety, Tolerability, Immunogenicity, and Potential Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

		Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial • Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

		• Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

TABLE OF CONTENTS

LIST OF TABLES 10
1. PROTOCOL SUMMARY 12
1.1. Synopsis 12
1.2. Schema 17
1.3. Schedule of Activities 18
1.3.1. Stage 1 Sentinel Cohorts 18
1.3.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts 22
1.3.3. Stage 3 Cohort(s) 24
2. INTRODUCTION 26
2.1. Study Rationale 26
2.2. Background 26
2.2.1. Clinical Overview 27
2.3. Benefit/Risk Assessment 27
2.3.1. Risk Assessment 29
2.3.2. Benefit Assessment 30
2.3.3. Overall Benefit/Risk Conclusion 30
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 30
4. STUDY DESIGN 32
4.1. Overall Design 32
4.1.1. Stage 1 33
4.1.2. Stage 2 34
4.1.3. Stage 3 34
4.2. Scientific Rationale for Study Design 34
4.3. Justification for Dose 35
4.4. End of Study Definition 35
5. STUDY POPULATION 36
5.1. Inclusion Criteria 36
5.2. Exclusion Criteria 37
5.3. Lifestyle Considerations 39

5.3.1. Contraception....39
5.4. Screen Failures....39
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration....40
6. STUDY INTERVENTION....40
6.1. Study Intervention(s) Administered....45
6.1.1. Administration....46
6.2. Preparation/Handling/Storage/Accountability....46
6.2.1. Preparation and Dispensing....47
6.3. Measures to Minimize Bias: Randomization and Blinding....47
6.3.1. Allocation to Study Intervention....47
6.3.2. Blinding of Site Personnel....48
6.3.3. Blinding of the Sponsor....48
6.3.4. Breaking the Blind....48
6.4. Study Intervention Compliance....49
6.5. Concomitant Therapy....49
6.5.1. Prohibited During the Study....49
6.5.2. Permitted During the Study....50
6.6. Dose Modification....50
6.7. Intervention After the End of the Study....50
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL....50
7.1. Discontinuation of Study Intervention....50
7.2. Participant Discontinuation/Withdrawal From the Study....51
7.2.1. Withdrawal of Consent....51
7.3. Lost to Follow-up....52
8. STUDY ASSESSMENTS AND PROCEDURES....52
8.1. Efficacy and/or Immunogenicity Assessments....53
8.1.1. Biological Samples....54
8.2. Safety Assessments....55
8.2.1. Clinical Safety Laboratory Assessments (Sentinel-Cohort Participants Only)....55

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.2.2. Electronic Diary 56
8.2.2.1. Grading Scales 56
8.2.2.2. Local Reactions 56
8.2.2.3. Systemic Events 57
8.2.2.4. Fever 58
8.2.2.5. Antipyretic Medication 59
8.2.3. Stopping Rules 59
8.2.3.1. Randomization and Vaccination After a Stopping Rule Is Met 60
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 Disease 60
8.2.5. Pregnancy Testing 61
8.3. Adverse Events and Serious Adverse Events 61
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 61
8.3.1.1. Reporting SAEs to Pfizer Safety 62
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 62
8.3.2. Method of Detecting AEs and SAEs 62
8.3.3. Follow-up of AEs and SAEs 63
8.3.4. Regulatory Reporting Requirements for SAEs 63
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 63
8.3.5.1. Exposure During Pregnancy 64
8.3.5.2. Exposure During Breastfeeding 65
8.3.5.3. Occupational Exposure 66
8.3.6. Medication Errors 66
8.4. Treatment of Overdose 67
8.5. Pharmacokinetics 67
8.6. Pharmacodynamics 67
8.7. Genetics 68
8.8. Biomarkers 68
8.9. Immunogenicity Assessments 68
8.10. Health Economics 68

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.11. Study Procedures 68
8.11.1. Stage 1 Sentinel Cohorts 68
8.11.1.1. Screening: (0 to 14 Days Before Visit 1) 68
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 69
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 71
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 73
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 74
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 76
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 77
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 78
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 4) 79
8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4) 79
8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4) 80
8.11.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts 80
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 80
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1) 82
8.11.2.3. Visit 3 – 2-Week Follow-up Visit: (12 to 16 Days After Visit 2) 84
8.11.2.4. Visit 4 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 2) 85
8.11.2.5. Visit 5 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 2) 85
8.11.2.6. Visit 6 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2) 86
8.11.2.7. Visit 7 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2) 86
8.11.3. Stage 3 Cohort(s) 86

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

8.11.3.1. Visit 1 – Vaccination 1: (Day 1) 86
8.11.3.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)....89
8.11.3.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)....90
8.11.3.4. Visit 4 – 6-Month Safety Telephone Contact: (154 to 168 Days After Visit 2) 91
8.11.3.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)....92
8.11.3.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)....92
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 92
8.13. COVID-19 Disease Surveillance (All Participants)....93
8.13.1. Potential COVID-19 Illness Telehealth Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)....94
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)....95
9. STATISTICAL CONSIDERATIONS 95
9.1. Estimands and Statistical Hypotheses 96
9.1.1. Estimands....96
9.1.2. Statistical Hypotheses....96
9.2. Sample Size Determination....96
9.3. Analysis Sets 97
9.4. Statistical Analyses 98
9.4.1. Immunogenicity Analyses 98
9.4.2. Efficacy Analyses 101
9.4.3. Safety Analyses 102
9.4.4. Other Analyses....103
9.5. Interim Analyses 104
9.5.1. Analysis Timing....104
9.6. Data Monitoring Committee or Other Independent Oversight Committee....104
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 106
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 106

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeupm.eu

10.1.1. Regulatory and Ethical Considerations 106
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 106
10.1.2. Informed Consent Process 107
10.1.3. Data Protection 108
10.1.4. Dissemination of Clinical Study Data 108
10.1.5. Data Quality Assurance 109
10.1.6. Source Documents 111
10.1.7. Study and Site Start and Closure 111
10.1.8. Sponsor's Qualified Medical Personnel 112
10.2. Appendix 2: Clinical Laboratory Tests 113
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 115
10.3.1. Definition of AE 115
10.3.2. Definition of SAE 116
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 118
10.3.4. Reporting of SAEs 121
10.4. Appendix 4: Contraceptive Guidance 122
10.4.1. Male Participant Reproductive Inclusion Criteria 122
10.4.2. Female Participant Reproductive Inclusion Criteria 122
10.4.3. Woman of Childbearing Potential 123
10.4.4. Contraception Methods 124
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 126
10.6. Appendix 6: Abbreviations 128
11. REFERENCES 131

LIST OF TABLES

Table 1. Potential Groups in Stage 1 41
Table 2. Local Reaction Grading Scale 57
Table 3. Systemic Event Grading Scale 58
Table 4. Scale for Fever 59

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 97
Table 6. Laboratory Abnormality Grading Scale 113

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2 Study to Describe the Safety, Tolerability, Immunogenicity, and Potential Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no vaccines to prevent infection with SARS-CoV-2 or antiviral drugs to treat COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on 1 of 3 RNA platforms: unmodified messenger RNA (uRNA, BNT162a), nucleoside-modified messenger RNA (modRNA, BNT162b), or self-amplifying messenger RNA (saRNA, BNT162c). Each vaccine candidate expresses 1 of 3 antigens: the SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein (P2 S) (version 9), a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5) or a membrane-anchored RBD. The 5 SARS-CoV-2 vaccine candidates that may be tested in this study are therefore:

BNT162a1 (variant RBL063.3): a uRNA encoding the RBD;

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S;

BNT162b3: a modRNA encoding a membrane-anchored RBD;

BNT162c2 (variant RBS004.2): an saRNA encoding the P2 S.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and potential efficacy of these 5 prophylactic BNT162 vaccines against COVID-19.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

It is expected that the various candidate vaccines may not all be available from the start of the study, in which case they will be rolled into the study in a consecutive fashion as they are released. A Phase 1/2 study of the same vaccine candidates (BNT162-01), conducted in Germany by BioNTech in adults 18 to 55 years of age, is planned to start in April 2020. Study C4591001 is designed to complement and expand upon the German study and confirm the optimal vaccine candidate(s) (BNT162a1, BNT162b1, BNT162b2, BNT162b3, or BNT162c2), dose level(s), number of doses, and schedule of administration.

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, in sentinel cohorts from Stage 1, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: ***Stage 1 Sentinel Cohorts:*** 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts:*** 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 3 Cohort(s):*** 1, 12, and 24 months after Dose 2	

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 serum neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 S1-specific binding antibody levels and RBD-specific binding antibody levels
To evaluate the efficacy of prophylactic BNT162 vaccines against confirmed COVID-19	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 serum neutralizing titers to the geometric mean of SARS-CoV-2–specific binding antibody levels at each time point In participants complying with the key protocol criteria (evaluable participants) following receipt of the last dose of study intervention: 100 × (1 – illness rate ratio) [ratio of active vaccine to placebo]	• SARS-CoV-2 serum neutralizing titers • SARS-CoV-2 S1-specific binding antibody levels • SARS-CoV-2 RBD-specific binding antibody levels COVID-19 incidence per 1000 person-years of follow-up
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
To describe the relationship between SARS-CoV-2 serological parameters and: • NAAT-confirmed COVID-19 • Symptomatic SARS-CoV-2 infection • Asymptomatic SARS-CoV-2 infection		Nonvaccine antigen SARS-CoV-2 antibody levels

Overall Design

This is a Phase 1/2, randomized, placebo-controlled, observer-blind, dose-finding, and vaccine candidate–selection study in healthy adults.

The study will evaluate the safety, tolerability, immunogenicity, and potential efficacy of up to 5 different SARS-CoV-2 RNA vaccine candidates against COVID-19:

- As a 2-dose (separated by 21 or 60 days) or single-dose schedule

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- At various different dose levels

- In 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age])

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study consists of 3 stages. Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3: a final candidate/dose large-scale stage. These stages, and the progression between them, are detailed in the schema (Section 1.2).

Number of Participants

Each group in Stage 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this stage, assuming 2 dose levels are selected following the initial dose escalation, up to 56 potential groups are foreseen; if all groups are fully enrolled, this corresponds to a total of 840 participants.

Each group in Stage 2 will comprise 225 participants (180 receiving active vaccine and 45 receiving placebo). The total number of participants to be enrolled in this stage depends on the number of groups to be pursued.

The vaccine candidate/dose level selected for Stage 3 will comprise 3000 participants. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study may evaluate single-dose and 2-dose (separated by 21 or 60 days) schedules of various different dose levels of up to 5 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age]):

- BNT162a1 (RNA-LNP vaccine utilizing uRNA and encoding the RBD): 0.1 µg, 0.3 µg, 1 µg

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 30 µg, 50 µg, 100 µg

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 30 µg, 50 µg, 100 µg

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- BNT162b3 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding a membrane-anchored RBD): 10 µg, 30 µg, 50 µg, 100 µg

- BNT162c2 (BNT162 RNA-LNP vaccine utilizing saRNA and encoding the RBD): 0.1 µg, 0.3 µg, 1 µg

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Stage 1 and Stage 2 dosing arms that are not evaluated in Stage 3.

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The study sample size for the first 2 stages of the study is not based on any statistical hypothesis testing. For the third stage, with assumptions of a true vaccine efficacy (VE) of 70%, 53 cases of COVID-19 will provide 98% power to conclude true VE >20%. This would be achieved with 3000 participants per group, based on the assumption of a 1.7% incidence rate in the placebo group, and 20% of the participants being nonevaluable.

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, abnormal hematology and chemistry laboratory parameters (sentinel cohorts only), and AEs and SAEs, for each vaccine group. A 3-tier approach will be used to summarize AEs.

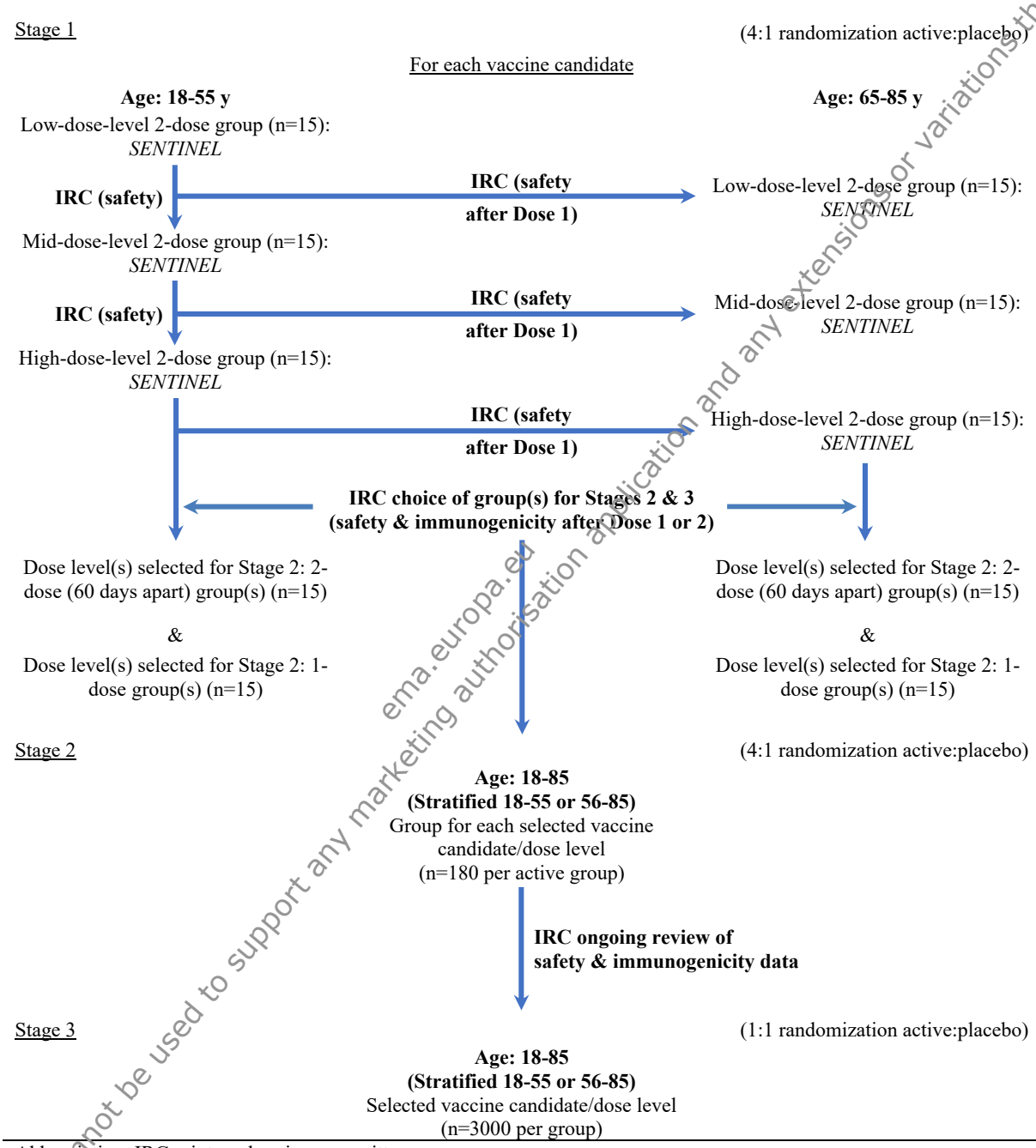
The secondary immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 serum neutralizing titers, SARS-CoV-2 S1-specific binding antibody levels, and RBD-specific binding antibody levels at the various time points.

For the secondary efficacy objective, VE is defined as VE = 100 × (1 – IRR), where IRR is the illness rate ratio, the calculated ratio of COVID-19 incidence in the active vaccine group to the incidence in the placebo group. The null hypothesis (VE ≤ 20%) will be rejected if the lower bound of the 95% CI for VE is >20%; no interim analysis of VE is planned.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.2. Schema



Abbreviation: IRC = internal review committee.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Stage 1 Sentinel Cohorts

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[a]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[b]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL		~50 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[c]		X			X								
Provide participant with 7-day e-diary, thermometer, and measuring device		X			X								
Review e-diary data (daily review is optimal during the active diary period)		◄	———	►	◄	———	►						
Review ongoing e-diary symptoms and obtain stop dates					X		X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collect e-diary or assist the participant to delete application							X						
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
b. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
c. The first 5 participants in in each sentinel group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 7 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	1	2	3	4	5	6	7	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**12 to 16 Days After Visit 2**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X								
Assign participant number	X								
Obtain demography and medical history data	X								
Perform physical examination	X								
Measure vital signs	X								
Perform urine pregnancy test (if appropriate)	X	X							
Collect nonstudy vaccine information	X	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X	X
Confirm eligibility	X	X							
Measure temperature (body)	X	X							
Review temporary delay criteria	X	X							
Confirm use of contraceptives (if appropriate)	X	X	X	X					
Obtain randomization number and study intervention allocation	X								

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	7	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**12 to 16 Days After Visit 2**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL		~50 mL
Obtain nasal (midturbinate) swab	X	X						X	
Administer study intervention	X	X							
Assess acute reactions for at least 30 minutes after study intervention administration	X	X							
Provide participant with 7-day e-diary, thermometer, and measuring device	X	X							
Review e-diary data (daily review is optimal during the active diary period)	←→	←→							
Review ongoing e-diary symptoms and obtain stop dates		X	X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application			X						
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)								X	X

Abbreviation: e-diary = electronic diary.

a. The window for Visit 2 is dependent on the dosing schedule for the assigned group.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Stage 3 Cohort(s)

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	1	2	3	4	5	6	Unplanned 3	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Safety Telephone Contact**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform physical examination	X							
Measure vital signs	X							
Perform urine pregnancy test (if appropriate)	X	X						
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Measure temperature (body)	X	X						
Review temporary delay criteria	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Obtain randomization number and study intervention allocation	X							
Collect blood sample for immunogenicity assessment	~50 mL		~50 mL		~50 mL	~50 mL		~50 mL
Obtain nasal (midturbinate) swab	X	X					X	

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Safety Telephone Contact**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Administer study intervention	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Provide participant with 7-day e-diary, thermometer, and measuring device	X	X						
Review e-diary data (daily review is optimal during the active diary period)	←→	←→						
Review ongoing e-diary symptoms and obtain stop dates		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application			X					
Telephone contact				X				
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviation: e-diary = electronic diary.

a. The window for Visit 2 is dependent on the dosing schedule(s) selected for the Stage 3.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy adults.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, immunogenicity, and potential efficacy of up to 5 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19 in healthy adults. There are currently no vaccines to prevent infection with SARS-CoV-2 or antiviral drugs to treat COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Five SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines utilizing different RNA formats may be evaluated in this study. Each vaccine candidate is based on 1 of 3 RNA platforms: unmodified messenger RNA (uRNA, BNT162a), nucleoside-modified messenger RNA (modRNA, BNT162b), or self-amplifying messenger RNA (saRNA, BNT162c). Each vaccine candidate expresses 1 of 3 antigens: the SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein (P2 S) (version 9), a trimerized SARS-CoV-2 spike glycoprotein receptor binding domain (RBD) (version 5), or a membrane-anchored RBD. The 5 SARS-CoV-2 vaccine candidates that may be tested in this study are therefore:

- **BNT162a1** (variant RBL063.3): uridine-containing unmodified messenger RNA (uRNA) with high intrinsic adjuvanticity, encoding the RBD.
- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.
- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above but encoding P2 S.
- **BNT162b3**: nucleoside-modified messenger RNA (modRNA) as above but encoding a membrane-anchored RBD.
- **BNT162c2** (variant RBS004.2): self-amplifying messenger RNA (saRNA) encoding the P2 S, in which higher amounts of protein per injected RNA template can be produced.

2.2.1. Clinical Overview

BNT162 vaccines have not been administered to humans before and thus there are no previous clinical data with these specific vaccines. However, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines are expected to have a favorable safety profile with mild, localized, and transient effects.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there are currently no data available from clinical trials on the use of BNT162 vaccines in humans, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, support a favorable risk/benefit profile. Anticipated AEs after vaccination are expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates support initiation of this Phase 1/2 clinical study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the investigator's brochure (IB), which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The study design includes the use of sentinel cohorts and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of an e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place for sentinel cohorts. The first 5 sentinel-cohort participants in each group will be observed for 4 hours after vaccination to assess any immediate AEs.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The study design includes the use of sentinel cohorts and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC and DMC will also review safety data throughout the study. Stopping rules are also in place for sentinel cohorts. The first 5 sentinel cohort participants in each group will be observed for 4 hours after vaccination to assess any immediate AEs.
Potential for COVID-19 disease enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	The study excludes participants with likely previous or current COVID-19. All participants are followed for SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 serum neutralizing titers, and COVID-19 illness, including markers of severity.
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of a potentially efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic and antibody testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, in sentinel cohorts from Stage 1, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: ***Stage 1 Sentinel Cohorts:*** 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts:*** 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 3 Cohort(s):*** 1, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 serum neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 S1-specific binding antibody levels and RBD-specific binding antibody levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 serum neutralizing titers to the geometric mean of SARS-CoV-2–specific binding antibody levels at each time point	• SARS-CoV-2 serum neutralizing titers • SARS-CoV-2 S1-specific binding antibody levels • SARS-CoV-2 RBD-specific binding antibody levels
To evaluate the efficacy of prophylactic BNT162 vaccines against confirmed COVID-19[x]	In participants complying with the key protocol criteria (evaluable participants) following receipt of the last dose of study intervention: 100 × (1 – illness rate ratio) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Objectives	Estimands	Endpoints
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
To describe the relationship between SARS-CoV-2 serological parameters and: • NAAT-confirmed COVID-19 • Symptomatic SARS-CoV-2 infection • Asymptomatic SARS-CoV-2 infection		Nonvaccine antigen SARS-CoV-2 antibody levels

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1/2, randomized, placebo-controlled, observer-blind, dose-finding, and vaccine candidate–selection study in healthy adults.

The study will evaluate the safety, tolerability, immunogenicity, and potential efficacy of up to 5 different SARS-CoV-2 RNA vaccine candidates against COVID-19:

- As a 2-dose (separated by 21 or 60 days) or single-dose schedule
- At various different dose levels
- In 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age])

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study consists of 3 stages. Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3; a final candidate/dose large-scale stage. These stages, and the progression between them, are detailed in the schema (Section 1.2).

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Stage 1 and Stage 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

4.1.1. Stage 1

Each group (vaccine candidate/dose level/age group/number of doses) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo. On Day 22, those in 2-dose groups will receive the same vaccine they received on Day 1; for those in single-dose groups, all will receive placebo. Full details of all potential groups in Stage 1 may be found in Table 1.

For each vaccine candidate/dose level/age group, the 15 participants randomized into each 2-dose group will comprise a sentinel cohort, to which the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment:
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Note that, for candidates based upon the same RNA platform (eg, BNT162b1, BNT162b2, and BNT162b3), dose escalation for the second and subsequent candidates studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the same RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

Once the IRC has selected a vaccine candidate/dose level to proceed into Stage 2, for each age cohort, 2 additional groups will be enrolled into Stage 1 for that vaccine candidate/dose level:

- A 2-dose group, with the 2 doses administered 60 days apart rather than 21

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- A 1-dose group

In this stage, assuming 2 dose levels are selected following the initial dose escalation, up to 56 potential groups are foreseen; if all groups are fully enrolled, this corresponds to a total of 840 participants.

4.1.2. Stage 2

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 or more groups (vaccine candidate/dose level) may be selected to proceed into Stage 2. Participants in this stage will be 18 to 85 years of age, stratified equally: 18 to 55 or 56 to 85 years. Commencement of each age stratum will be dependent upon satisfactory safety and immunogenicity data from the 18- to 55-year and 65- to 85-year groups from Stage 1, respectively. It is therefore possible that the 2 age strata may not start concurrently.

In each group selected for Stage 2, it is intended that 225 participants will be randomized in a 4:1 ratio to receive active vaccine (180 participants) or placebo (45 participants).

4.1.3. Stage 3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 group may be selected to proceed into Stage 3. Participants in this stage will be 18 to 85 years of age, stratified equally: 18 to 55 years or 56 to 85 years. As in Stage 2, it is possible that the 2 age strata may not start concurrently.

The vaccine candidate/dose level selected for Stage 3 will comprise 3000 participants. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Stage 1 and Stage 2 dosing arms that are not evaluated in Stage 3.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences respiratory symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data are not currently available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting doses of 3 µg (for BNT162a1 and BNT162c2) and 10 µg (for BNT162b1 and BNT162b2) in this study were based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components (uRNA, modRNA, saRNA), with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 1: preliminary experience in the BioNTech study conducted in Germany (BNT162-01), following vaccination of 6 participants with 3 µg of BNT162a1, demonstrated an undesirable level of systemic reactogenicity. Therefore, potential dose levels for BNT162a1 and BNT162c2 (which are both based upon unmodified RNA) dependent upon further data from the BNT162-01 study, are each reduced 30-fold to 0.1 µg, 0.3 µg, and 1 µg.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1, BNT162b2, and BNT162b3.

Taken together, the planned starting doses in this study in healthy participants are considered to be safe, but still sufficient to induce an antiviral immune response.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Stages 1 and 2 in groups that do not proceed to Stage 3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, 65 and 85 years, inclusive, or 18 and 85 years, inclusive, at randomization (dependent upon study stage).

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.

Informed Consent:

4. Capable of giving personal signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. **Stages 1 and 2 only:** Previous clinical or microbiological diagnosis of COVID-19.

6. **Sentinel participants in Stage 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - Chronic liver disease
    - Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
    - Resident in a long-term facility
    - BMI >30 kg/m^2
    - Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Sentinel participants in Stage 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for sentinel participants in Stage 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Sentinel participants in Stage 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Sentinel participants in Stage 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.au

19. **Sentinel participants in Stage 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Sentinel participants in Stage 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Sentinel participants in Stage 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
   - New or increased cough;
   - New or increased shortness of breath;
   - New or increased sore throat;
   - New or increased wheezing;
   - New or increased sputum production;
   - New or increased nasal congestion;
   - New or increased nasal discharge;
   - Loss of taste/smell.
2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.
3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.
4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study may evaluate 2-dose (separated by 21 or 60 days) and single-dose schedules of various different dose levels of up to 5 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age]). These 5

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

investigational RNA vaccine candidates, with the addition of saline placebo, are the 6 potential study interventions that may be administered to a study participant:

- BNT162a1 (RNA-LNP vaccine utilizing uRNA and encoding the RBD): 0.1 µg, 0.3 µg, 1 µg
- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 30 µg, 50 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 30 µg, 50 µg, 100 µg
- BNT162b3 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding a membrane-anchored RBD): 10 µg, 30 µg, 50 µg, 100 µg
- BNT162c2 (BNT162 RNA-LNP vaccine utilizing saRNA and encoding the RBD): 0.1 µg, 0.3 µg, 1 µg
- Normal saline (0.9% sodium chloride solution for injection)

A list of all potential groups in the Stage 1 are shown in Table 1. Each of these groups may or may not progress to the later stages of the study.

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
2-Dose Groups (Sentinel Cohorts)			**Day 1**			**Day 22**		
a-0.1-2-Y (Sentinel) [uRNA 0.1 µg (2 doses)]	15	18 to 55	BNT162a1 Placebo	0.1 µg	(n=12) (n=3)	BNT162a1 Placebo	0.1 µg	(n=12) (n=3)
a-0.3-2-Y (Sentinel) [uRNA 0.3 µg (2 doses)]	15	18 to 55	BNT162a1 Placebo	0.3 µg	(n=12) (n=3)	BNT162a1 Placebo	0.3 µg	(n=12) (n=3)
a-1-2-Y (Sentinel) [uRNA 1 µg (2 doses)]	15	18 to 55	BNT162a1 Placebo	1 µg	(n=12) (n=3)	BNT162a1 Placebo	1 µg	(n=12) (n=3)
b1-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	10 µg	(n=12) (n=3)	BNT162b1 Placebo	10 µg	(n=12) (n=3)
b1-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	30 µg	(n=12) (n=3)	BNT162b1 Placebo	30 µg	(n=12) (n=3)
b1-50-2-Y (Sentinel) [modRNA 50 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	50 µg	(n=12) (n=3)	BNT162b1 Placebo	50 µg	(n=12) (n=3)
b1-100-2-Y (Sentinel) [modRNA 100 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	100 µg	(n=12) (n=3)	BNT162b1 Placebo	100 µg	(n=12) (n=3)
b2-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	10 µg	(n=12) (n=3)	BNT162b2 Placebo	10 µg	(n=12) (n=3)
b2-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	30 µg	(n=12) (n=3)	BNT162b2 Placebo	30 µg	(n=12) (n=3)
b2-50-2-Y (Sentinel) [modRNA 50 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	50 µg	(n=12) (n=3)	BNT162b2 Placebo	50 µg	(n=12) (n=3)

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
b2-100-2-Y (Sentinel) [modRNA 100 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	100 µg	(n=12) (n=3)	BNT162b2 Placebo	100 µg	(n=12) (n=3)
b3-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b3 Placebo	10 µg	(n=12) (n=3)	BNT162b3 Placebo	10 µg	(n=12) (n=3)
b3-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b3 Placebo	30 µg	(n=12) (n=3)	BNT162b3 Placebo	30 µg	(n=12) (n=3)
b3-50-2-Y (Sentinel) [modRNA 50 µg (2 doses)]	15	18 to 55	BNT162b3 Placebo	50 µg	(n=12) (n=3)	BNT162b3 Placebo	50 µg	(n=12) (n=3)
b3-100-2-Y (Sentinel) [modRNA 100 µg (2 doses)]	15	18 to 55	BNT162b3 Placebo	100 µg	(n=12) (n=3)	BNT162b3 Placebo	100 µg	(n=12) (n=3)
c-0.1-2-Y (Sentinel) [saRNA 0.1 µg (2 doses)]	15	18 to 55	BNT162c2 Placebo	0.1 µg	(n=12) (n=3)	BNT162c2 Placebo	0.1 µg	(n=12) (n=3)
c-0.3-2-Y (Sentinel) [saRNA 0.3 µg (2 doses)]	15	18 to 55	BNT162c2 Placebo	0.3 µg	(n=12) (n=3)	BNT162c2 Placebo	0.3 µg	(n=12) (n=3)
c-1-2-Y (Sentinel) [saRNA 1 µg (2 doses)]	15	18 to 55	BNT162c2 Placebo	1 µg	(n=12) (n=3)	BNT162c2 Placebo	1 µg	(n=12) (n=3)
a-0.1-2-O (Sentinel) [uRNA 0.1 µg (2 doses)]	15	65 to 85	BNT162a1 Placebo	0.1 µg	(n=12) (n=3)	BNT162a1 Placebo	0.1 µg	(n=12) (n=3)
a-0.3-2-O (Sentinel) [uRNA 0.3 µg (2 doses)]	15	65 to 85	BNT162a1 Placebo	0.3 µg	(n=12) (n=3)	BNT162a1 Placebo	0.3 µg	(n=12) (n=3)
a-1-2-O (Sentinel) [uRNA 1 µg (2 doses)]	15	65 to 85	BNT162a1 Placebo	1 µg	(n=12) (n=3)	BNT162a1 Placebo	1 µg	(n=12) (n=3)
b1-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	10 µg	(n=12) (n=3)	BNT162b1 Placebo	10 µg	(n=12) (n=3)
b1-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	30 µg	(n=12) (n=3)	BNT162b1 Placebo	30 µg	(n=12) (n=3)
b1-50-2-O (Sentinel) [modRNA 50 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	50 µg	(n=12) (n=3)	BNT162b1 Placebo	50 µg	(n=12) (n=3)
b1-100-2-O (Sentinel) [modRNA 100 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	100 µg	(n=12) (n=3)	BNT162b1 Placebo	100 µg	(n=12) (n=3)
b2-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	10 µg	(n=12) (n=3)	BNT162b2 Placebo	10 µg	(n=12) (n=3)
b2-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	30 µg	(n=12) (n=3)	BNT162b2 Placebo	30 µg	(n=12) (n=3)
b2-50-2-O (Sentinel) [modRNA 50 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	50 µg	(n=12) (n=3)	BNT162b2 Placebo	50 µg	(n=12) (n=3)
b2-100-2-O (Sentinel) [modRNA 100 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	100 µg	(n=12) (n=3)	BNT162b2 Placebo	100 µg	(n=12) (n=3)
b3-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b3 Placebo	10 µg	(n=12) (n=3)	BNT162b3 Placebo	10 µg	(n=12) (n=3)
b3-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b3 Placebo	30 µg	(n=12) (n=3)	BNT162b3 Placebo	30 µg	(n=12) (n=3)

This document may not be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
b3-50-2-O (Sentinel) [modRNA 50 µg (2 doses)]	15	65 to 85	BNT162b3 Placebo	50 µg	(n=12) (n=3)	BNT162b3 Placebo	50 µg	(n=12) (n=3)
b3-100-2-O (Sentinel) [modRNA 100 µg (2 doses)]	15	65 to 85	BNT162b3 Placebo	100 µg	(n=12) (n=3)	BNT162b3 Placebo	100 µg	(n=12) (n=3)
c-0.1-2-O (Sentinel) [saRNA 0.1 µg (2 doses)]	15	65 to 85	BNT162c2 Placebo	0.1 µg	(n=12) (n=3)	BNT162c2 Placebo	0.1 µg	(n=12) (n=3)
c-0.3-2-O (Sentinel) [saRNA 0.3 µg (2 doses)]	15	65 to 85	BNT162c2 Placebo	0.3 µg	(n=12) (n=3)	BNT162c2 Placebo	0.3 µg	(n=12) (n=3)
c-1-2-O (Sentinel) [saRNA 1 µg (2 doses)]	15	65 to 85	BNT162c2 Placebo	1 µg	(n=12) (n=3)	BNT162c2 Placebo	1 µg	(n=12) (n=3)
Single-Dose Groups			**Day 1**			**Day 22**		
a-x-1-Y [uRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162a1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b1-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b2-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b3-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b3 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
c-x-1-Y [saRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162c2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
a-x-1-O [uRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162a1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b1-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b2-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b3-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b3 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
c-x-1-O [saRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162c2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
2-Dose Groups (Longer Schedule)			**Day 1**			**Day 61**		
a-x-2L-Y [uRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162a1 Placebo	TBD	(n=12) (n=3)	BNT162a1 Placebo	TBD	(n=12) (n=3)
b1-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b1 Placebo	TBD	(n=12) (n=3)	BNT162b1 Placebo	TBD	(n=12) (n=3)
b2-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b2 Placebo	TBD	(n=12) (n=3)	BNT162b2 Placebo	TBD	(n=12) (n=3)
b3-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b3 Placebo	TBD	(n=12) (n=3)	BNT162b3 Placebo	TBD	(n=12) (n=3)
c-x-2L-Y [saRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162c2 Placebo	TBD	(n=12) (n=3)	BNT162c2 Placebo	TBD	(n=12) (n=3)
a-x-2L-O [uRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162a1 Placebo	TBD	(n=12) (n=3)	BNT162a1 Placebo	TBD	(n=12) (n=3)
b1-x-2L-O [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162b1 Placebo	TBD	(n=12) (n=3)	BNT162b1 Placebo	TBD	(n=12) (n=3)
b2-x-2L-O [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162b2 Placebo	TBD	(n=12) (n=3)	BNT162b2 Placebo	TBD	(n=12) (n=3)
b3-x-2L-O [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162b3 Placebo	TBD	(n=12) (n=3)	BNT162b3 Placebo	TBD	(n=12) (n=3)
c-x-2L-O [saRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162c2 Placebo	TBD	(n=12) (n=3)	BNT162c2 Placebo	TBD	(n=12) (n=3)

Abbreviations: modRNA = nucleoside-modified messenger ribonucleic acid; saRNA = self-amplifying messenger ribonucleic acid; TBD = to be determined; uRNA = unmodified messenger ribonucleic acid.

This document is a draft to be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

6.1. Study Intervention(s) Administered

Intervention Name	BNT162a1 (BNT 162 RNA-LNP vaccine utilizing uRNA)	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b3 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162c2 (BNT162 RNA-LNP vaccine utilizing saRNA	Saline placebo
Type	Vaccine	Vaccine	Vaccine	Vaccine	Vaccine	Placebo
Dose Formulation	uRNA	modRNA	modRNA	modRNA	saRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	0.1-, 0.3-, 1-µg	10-, 30-, 50-, 100-µg	10-, 30-, 50-, 100-µg	10-, 30-, 50-, 100-µg	0.1-, 0.3-, 1-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

6.1.1. Administration

Participants will receive 1 dose (0.5 mL) of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Stage 1 sentinel cohort participants, Visits 1 and 2 for all other participants) in accordance with the study's SoA.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Stage 1 and in Stage 2. Sponsor staff will be blinded to study intervention allocation in Stage 3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study.

Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate). Unblinded clinician(s) who are not direct members of the study team will review unblinded protocol deviations.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Stage 1 sentinel cohorts, Visit 5 for Stage 1 nonsentinel cohorts and Stage 2 participants, and Visit 4 for Stage 3 participants).

- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

- In addition, for participants enrolled in the Stage 1 sentinel cohorts, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 for Stage 1 sentinel cohorts, Visit 4 for Stage 1 nonsentinel cohorts and Stage 2 participants, and Visit 3 for Stage 3 participants).

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Stage 1 sentinel cohorts.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Stage 1 sentinel cohorts – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

Individual participant dose modifications will not be made in this study.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria).

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 530 mL for participants in the Stage 1 sentinel cohorts; 350 mL for participants in the Stage 1 nonsentinel cohorts and Stage 2 participants; and 200 mL for Stage 3 participants. Additionally, 50 mL of blood will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, a telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. Four definitions of potential SARS-CoV-2–related cases will be considered:

- Centrally confirmed COVID-19: presence of at least 1 symptom described in Section 8.13 and SARS-CoV-2 NAAT positive at central laboratory

- Locally confirmed COVID-19: presence of at least 1 symptom described in Section 8.13 and investigator-confirmed SARS-CoV-2 NAAT positive at a local testing facility

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Centrally confirmed symptomatic seroconversion to SARS-CoV-2 (exploratory): presence of at least 1 symptom described in Section 8.13 and a positive nonvaccine antigen SARS-CoV-2 antibody result in a participant whose most recent prior nonvaccine antigen SARS-CoV-2 antibody result was negative

- Centrally confirmed asymptomatic seroconversion to SARS-CoV-2 (exploratory): positive nonvaccine antigen SARS-CoV-2 antibody result in a participant with a prior nonvaccine antigen SARS-CoV-2 antibody result was negative

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 serum neutralization assay

- SARS-CoV-2 S1-specific IgG direct Luminex immunoassay

- SARS-CoV-2 RBD-specific IgG direct Luminex immunoassay

- Nonvaccine antigen (NVA) Ig direct Luminex immunoassay. The NVA will include a SARS-CoV-2 target antigen that is not derived from the S glycoprotein, most likely an antigen derived from the SARS-CoV-2 nucleoprotein.

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Stage 1 sentinel cohorts (see Section 8.11.1.1) to determine eligibility.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Stage 1 sentinel group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2.

8.2.1. Clinical Safety Laboratory Assessments (Sentinel-Cohort Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

8.2.2. Electronic Diary

Participants will be required to complete an e-diary through an application installed on a provisioned device or on the participant's own personal device. The participant will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. The e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

8.2.2.2. Local Reactions

During the e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary. If a local reaction persists beyond the end of the e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 2. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 2.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

If a Grade 3 local reaction is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 3.

If a Grade 3 systemic event is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Table 3. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the e-diary in the evening daily during the e-diary reporting period. It will also be collected at any time during the e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 4.

If a fever of ≥39.0°C (102.1°F) is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Table 4. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Stopping Rules

The following stopping rules are in place for all Stage 1 sentinel-cohort participants, based on review of AE data and e-diary reactogenicity data. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during the Stage 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. E-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

BNT162 RNA platforms (ie, a, b, and c) will be evaluated for contribution to stopping rules individually; vaccine candidate dose levels within a platform and age groups will contribute

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19 disease.

8.2.3.1. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC and DMC have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 Disease

As this is a sponsor open-label study during Stages 1 and 2, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment.

Participants in all stages of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13). All NAAT-confirmed cases will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6). In addition, instances of symptomatic and asymptomatic seroconversion to SARS-CoV-2 (see Section 8.1) will be reviewed.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater severity, compared to available information at the time of

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review. Since the DMC is able to review unblinded information, it will also be able to compare cases in active vaccine and placebo recipients in Stage 3 (when sponsor staff will be blinded).

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Stage 1 sentinel-cohort participants, Visit 4 for Stage 1 nonsentinel participants and Stage 2 participants, and Visit 3 for Stage 3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Stage 1 sentinel-

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

cohort participants, Visit 5 for Stage 1 nonsentinel cohort participants and Stage 2 participants, and Visit 4 for Stage 3 participants).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccines SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccines SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccines SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are recorded on the CRF. AEs and SAEs that begin after obtaining informed consent but before the start of study intervention will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section. AEs and SAEs that begin after the start of study intervention are recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccines SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccines SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccines SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

This document cannot be used to support any marketing authorisation application. ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccines SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

8.3.6. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccines SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

8.11.1. Stage 1 Sentinel Cohorts

8.11.1.1. Screening: (0 to 14 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.5.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.

- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- The first 5 participants vaccinated in each Stage 1 sentinel group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Explain the e-diary technologies available for this study, and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

  Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy (see Section 7.1).

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (≥20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study, and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)

The window for Visit 2 is dependent on the dosing schedule for the assigned group.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy (see Section 7.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 2-Week Follow-up Visit: (12 to 16 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

8.11.2.4. Visit 4 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.5. Visit 5 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.7. Visit 7 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.3. Stage 3 Cohort(s)

8.11.3.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document can only be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Explain the e-diary technologies available for this study, and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

8.11.3.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)

The window for Visit 2 is dependent on the dosing schedule(s) selected for Stage 3.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.3.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.

- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.

- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.3.4. Visit 4 – 6-Month Safety Telephone Contact: (154 to 168 Days After Visit 2)

- Contact the participant by telephone in order to obtain the following information.
- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

8.11.3.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.3.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Disease Surveillance (All Participants)

If a participant experiences any of the following, he or she is instructed to contact the site immediately, and if confirmed, participate in a telehealth visit as soon as possible, optimally within 3 days of symptom onset. Note that this does not substitute for a participant's routine medical care. Therefore participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- New or increased sore throat;
- New or increased wheezing;
- New or increased sputum production;
- New or increased nasal congestion;
- New or increased nasal discharge;
- Loss of taste/smell.

8.13.1. Potential COVID-19 Illness Telehealth Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This telehealth visit is expected to involve the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several telehealth contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory. The result from this swab will be provided to the site once it is available, but this will not be in real time, and cannot be relied upon to direct clinical care. Therefore, the participant should be encouraged to seek care, if appropriate, from his or her usual provider.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
    - Symptoms
    - Clinical diagnosis

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Local laboratory COVID-19 test result
- Full blood count
- C-reactive protein
- Number and type of any healthcare contact; duration of hospitalization and intensive care unit stay
- Need for oxygen therapy
- Need for ventilation

- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

At the end of Stage 3, the vaccine efficacy (VE) will be evaluated. VE is defined as VE = 100 × (1 – IRR), where IRR is the illness rate ratio, the calculated ratio of the COVID-19 illness rate in the active vaccine group to the incidence rate in the placebo group. The efficacy hypothesis is:

H_0: VE ≤20% vs H_a: VE >20%

where H_0 and H_a represent null hypothesis and alternative hypothesis. For participants with multiple illnesses, only the first COVID-19 confirmed case will contribute to the VE calculation in the hypothesis test.

The efficacy will be demonstrated if the null hypothesis VE ≤20% is rejected at the 0.025 significance level, that is, when the lower limit of the 2-sided 95% CI for VE is >20%, which is derived using the Clopper-Pearson method as described by Agresti.[9]

9.2. Sample Size Determination

The study sample size for the first 2 stages of the study is not based on any statistical hypothesis testing. Stage 1 will comprise 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; up to 56 potential groups are foreseen; if all groups are fully enrolled, assuming 2 dose levels are selected following the initial dose escalation, this corresponds to a total of 840 participants. Stage 2 will include 1 or

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

more vaccine groups selected from Stage 1, and 225 participants will be randomized per selected vaccine candidate in a 4:1 ratio to receive active vaccine (180 participants) or placebo (45 participants).

For Stage 3, for the selected vaccine candidate/dose level, with assumptions of a true vaccine efficacy (VE) of 70%, 53 cases of COVID-19 will provide 90% power to conclude true VE >20%. This would be achieved with 3000 participants per group (1:1 randomization ratio), based on the assumption of a 1.7% incidence rate in the placebo group, and 20% of the participants being nonevaluable.

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=3000
0.10%	0.01	0.04	0.16	0.95
0.50%	0.06	0.20	0.59	>0.99
1.00%	0.11	0.36	0.84	>0.99
2.00%	0.22	0.60	0.97	>0.99
3.00%	0.31	0.75	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	All eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result 21 days after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other major protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Population	Description
	immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other major protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive vaccination(s) as randomized within the predefined window, have the efficacy measurement after the last dose of study intervention, and have no other major protocol deviations as determined by the clinician.
All-available efficacy	All eligible randomized participants who receive at least 1 vaccination and have the efficacy measurement at any time after Dose 1.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific binding antibody levels and RBD-specific binding antibody levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product (active/placebo) within each group before vaccination and at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 12, and 24 months after Dose 2 Geometric means and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on the t-distribution, and then exponentiating the results. **GMFRs of SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific antibody levels and RBD-specific binding antibody levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and transformed back to the original scale. Two-sided CIs will be obtained by

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Endpoint	Statistical Analysis Methods
	calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and transforming the limits back to the original scale. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific antibody levels and RBD-specific binding antibody levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 serum neutralizing titer to SARS-CoV-2 S1-specific antibody and SARS-CoV-2 RBD-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific binding antibody levels and RBD-specific binding antibody levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 Cohort(s): 1, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Endpoint	Statistical Analysis Methods
	antibody/SARS-CoV-2 RBD-specific binding antibody at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 serum neutralizing titers minus SARS-CoV-2 S1-specific antibody for each participant) and transformed back to the original scale. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and transforming the limits back to the original scale. The same analysis methods will be applied to the immunogenicity endpoints in Stages 2 and 3. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Tertiary/ exploratory immunogenicity	**Correlation of an RT-PCR–confirmed COVID-19 infection and seropositivity/seroconversion measured by nonvaccine antigen SARS-CoV-2 antibody** If sufficient data are collected, percentages (and 2-sided 95% CIs) of participants with confirmed COVID-19 and nonvaccine antigen SARS-CoV-2 antibody levels after Dose 1 and after Dose 2 will be provided. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 serum neutralizing titers, SARS-CoV-2 S1-specific antibody, and RBD-specific binding antibody after Dose 1 and after Dose 2.

9.4.2. Efficacy Analyses

The statistical analysis of efficacy will be based on the evaluable efficacy population (primary analysis) and the all-available efficacy population as defined in Section 9.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Endpoint	Statistical Analysis Methods
Secondary efficacy	**Ratio of COVID-19 incidence per 1000 person-years of follow-up for the active vaccine group to the placebo group** Vaccine efficacy will be estimated by 100 × (1 – IRR), where IRR is the illness rate ratio, the calculated ratio of COVID-19 infection incidence per 1000 person-years follow-up in the active vaccine group to the corresponding incidence in the placebo group after 2 doses. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. For the primary analysis, missing efficacy data will not be imputed. A sensitivity analysis may be performed by imputing missing values; details will be provided in the SAP.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	• Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. • For Stage 1 sentinel cohorts, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. • AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Endpoint	Statistical Analysis Methods
	term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. • Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. • SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after last dose will be provided for each vaccine group. • The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	• Not applicable (N/A)
Exploratory	• N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 serum neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the SARS-CoV-2 S1-specific binding antibody level at the postvaccination time point to the corresponding antibody level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the SARS-CoV-2 RBD-specific binding antibody level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

9.5. Interim Analyses

No formal interim analysis is planned in this study. As this is a sponsor open-label study during Stages 1 and 2, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 3 weeks after Dose 2 for Stage 1.
- Complete safety and immunogenicity analysis approximately 3 weeks after Dose 2 for Stage 2.
- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3.
- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available at the end of the study.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC and a DMC. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met
- Review of safety and/or immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate(s)/dose level(s) and schedule(s) to proceed into Stage 2. Data supporting the selection, including results for both binding antibody levels and serum neutralizing titers, and the ratio between them, will also be submitted to the FDA for review
  - Select vaccine candidate(s)/dose level(s) and schedule(s) to proceed into Stage 3. Data supporting the selection, including results for both binding antibody levels and

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

serum neutralizing titers, and the ratio between them, will also be submitted to the FDA for review

- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 6).

Table 6. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Table 6. Laboratory Abnormality Grading Scale

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
Chemistry	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccines SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccines SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccines SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and EDP supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccines SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccines SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccines SAE Report Form
• Facsimile transmission of the Vaccines SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccines SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccines SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use application
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

Abbreviation	Term
HBc Ab	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
modRNA	nucleoside-modified messenger ribonucleic acid
N/A	not applicable
NAAT	nucleic acid amplification test
NVA	nonvaccine antigen
P2 S	SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein

This document cannot be used to support any marketing authorization application and any extensions or variations thereof

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Abbreviation	Term
PCR	polymerase chain reaction
PI	principal investigator
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): therapeutic options. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Accessed: 12 Apr 2020.

4 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

5 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

6 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

7 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine. 2019;37(25):3326-34.

8 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

9 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

10 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

Document Approval Record

Document Name:	C4591001 Final Clinical Protocol Amendment 2 , Clean copy, 27 May 2020
Document Title:	A PHASE 1/2, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO DESCRIBE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND POTENTIAL EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY ADULTS

Signed By:	Date(GMT)	Signing Capacity
PPD	29-May-2020 12:40:47	Business Line Approver
PPD	29-May-2020 13:08:07	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e1938f5b07\Approved\Approved On: 29-May-2020 13:08 (GMT)

A PHASE 1/2, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO DESCRIBE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND POTENTIAL EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY ADULTS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	N/A
Protocol Number:	C4591001
Phase:	1/2

Short Title: A Phase 1/2 Study to Describe the Safety, Tolerability, Immunogenicity, and Potential Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 1	13 May 2020	Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

		• Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial • Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

TABLE OF CONTENTS

LIST OF TABLES 9
1. PROTOCOL SUMMARY 11
1.1. Synopsis 11
1.2. Schema 16
1.3. Schedule of Activities 17
1.3.1. Stage 1 Sentinel Cohorts 17
1.3.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts 21
1.3.3. Stage 3 Cohort(s) 23
2. INTRODUCTION 25
2.1. Study Rationale 25
2.2. Background 25
2.2.1. Clinical Overview 26
2.3. Benefit/Risk Assessment 26
2.3.1. Risk Assessment 28
2.3.2. Benefit Assessment 29
2.3.3. Overall Benefit/Risk Conclusion 29
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 29
4. STUDY DESIGN 31
4.1. Overall Design 31
4.1.1. Stage 1 32
4.1.2. Stage 2 33
4.1.3. Stage 3 33
4.2. Scientific Rationale for Study Design 33
4.3. Justification for Dose 34
4.4. End of Study Definition 34
5. STUDY POPULATION 35
5.1. Inclusion Criteria 35
5.2. Exclusion Criteria 36
5.3. Lifestyle Considerations 38

5.3.1. Contraception....38
5.4. Screen Failures....38
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration....39
6. STUDY INTERVENTION....39
6.1. Study Intervention(s) Administered....43
6.1.1. Administration....44
6.2. Preparation/Handling/Storage/Accountability....44
6.2.1. Preparation and Dispensing....45
6.3. Measures to Minimize Bias: Randomization and Blinding....45
6.3.1. Allocation to Study Intervention....45
6.3.2. Blinding of Site Personnel....46
6.3.3. Blinding of the Sponsor....46
6.3.4. Breaking the Blind....46
6.4. Study Intervention Compliance....47
6.5. Concomitant Therapy....47
6.5.1. Prohibited During the Study....47
6.5.2. Permitted During the Study....48
6.6. Dose Modification....48
6.7. Intervention After the End of the Study....48
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL....48
7.1. Discontinuation of Study Intervention....48
7.2. Participant Discontinuation/Withdrawal From the Study....49
7.2.1. Withdrawal of Consent....49
7.3. Lost to Follow-up....50
8. STUDY ASSESSMENTS AND PROCEDURES....50
8.1. Efficacy and/or Immunogenicity Assessments....51
8.1.1. Biological Samples....52
8.2. Safety Assessments....53
8.2.1. Clinical Safety Laboratory Assessments (Sentinel-Cohort Participants Only)....53

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.2.2. Electronic Diary 54
8.2.2.1. Grading Scales 54
8.2.2.2. Local Reactions 54
8.2.2.3. Systemic Events 55
8.2.2.4. Fever 56
8.2.2.5. Antipyretic Medication 57
8.2.3. Stopping Rules 57
8.2.3.1. Randomization and Vaccination After a Stopping Rule Is Met 58
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 Disease 58
8.2.5. Pregnancy Testing 59
8.3. Adverse Events and Serious Adverse Events 59
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 59
8.3.1.1. Reporting SAEs to Pfizer Safety 60
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 60
8.3.2. Method of Detecting AEs and SAEs 60
8.3.3. Follow-up of AEs and SAEs 61
8.3.4. Regulatory Reporting Requirements for SAEs 61
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 61
8.3.5.1. Exposure During Pregnancy 62
8.3.5.2. Exposure During Breastfeeding 63
8.3.5.3. Occupational Exposure 64
8.3.6. Medication Errors 64
8.4. Treatment of Overdose 65
8.5. Pharmacokinetics 65
8.6. Pharmacodynamics 65
8.7. Genetics 66
8.8. Biomarkers 66
8.9. Immunogenicity Assessments 66
8.10. Health Economics 66

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.11. Study Procedures 66
8.11.1. Stage 1 Sentinel Cohorts 66
8.11.1.1. Screening: (0 to 14 Days Before Visit 1) 66
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 67
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 69
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 71
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 72
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 74
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 75
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 76
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 4) 77
8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4) 77
8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4) 78
8.11.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts 78
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 78
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1) 80
8.11.2.3. Visit 3 – 2-Week Follow-up Visit: (12 to 16 Days After Visit 2) 82
8.11.2.4. Visit 4 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 2) 83
8.11.2.5. Visit 5 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 2) 83
8.11.2.6. Visit 6 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2) 84
8.11.2.7. Visit 7 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2) 84
8.11.3. Stage 3 Cohort(s) 84

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.11.3.1. Visit 1 – Vaccination 1: (Day 1) 84
8.11.3.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)....86
8.11.3.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)....88
8.11.3.4. Visit 4 – 6-Month Safety Telephone Contact: (154 to 168 Days After Visit 2) 89
8.11.3.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)....89
8.11.3.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)....90
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 90
8.13. COVID-19 Disease Surveillance (All Participants)....91
8.13.1. Potential COVID-19 Illness Telehealth Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)....92
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)....93
9. STATISTICAL CONSIDERATIONS 93
9.1. Estimands and Statistical Hypotheses 93
9.1.1. Estimands....93
9.1.2. Statistical Hypotheses....94
9.2. Sample Size Determination....94
9.3. Analysis Sets 95
9.4. Statistical Analyses 96
9.4.1. Immunogenicity Analyses 96
9.4.2. Efficacy Analyses 99
9.4.3. Safety Analyses 100
9.4.4. Other Analyses....101
9.5. Interim Analyses 102
9.5.1. Analysis Timing....102
9.6. Data Monitoring Committee or Other Independent Oversight Committee....102
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 104
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 104

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

10.1.1. Regulatory and Ethical Considerations 104
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 104
10.1.2. Informed Consent Process 105
10.1.3. Data Protection 106
10.1.4. Dissemination of Clinical Study Data 106
10.1.5. Data Quality Assurance 107
10.1.6. Source Documents 109
10.1.7. Study and Site Start and Closure 109
10.1.8. Sponsor's Qualified Medical Personnel 110
10.2. Appendix 2: Clinical Laboratory Tests 111
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 113
10.3.1. Definition of AE 113
10.3.2. Definition of SAE 114
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 116
10.3.4. Reporting of SAEs 119
10.4. Appendix 4: Contraceptive Guidance 120
10.4.1. Male Participant Reproductive Inclusion Criteria 120
10.4.2. Female Participant Reproductive Inclusion Criteria 120
10.4.3. Woman of Childbearing Potential 120
10.4.4. Contraception Methods 121
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 123
10.6. Appendix 6: Abbreviations 125
11. REFERENCES 128

LIST OF TABLES

Table 1. Potential Groups in Stage 1 40
Table 2. Local Reaction Grading Scale 55
Table 3. Systemic Event Grading Scale 56
Table 4. Scale for Fever 57

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 95
Table 6. Laboratory Abnormality Grading Scale 111

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2 Study to Describe the Safety, Tolerability, Immunogenicity, and Potential Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no vaccines to prevent infection with SARS-CoV-2 or antiviral drugs to treat COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on 1 of 3 RNA platforms: unmodified messenger RNA (uRNA, BNT162a), nucleoside-modified messenger RNA (modRNA, BNT162b), or self-amplifying messenger RNA (saRNA, BNT162c). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 4 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

BNT162a1 (variant RBL063.3): a uRNA encoding the RBD;

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S;

BNT162c2 (variant RBS004.2): an saRNA encoding the P2 S.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and potential efficacy of these 4 prophylactic BNT162 vaccines against COVID-19.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

It is expected that the various candidate vaccines may not all be available from the start of the study, in which case they will be rolled into the study in a consecutive fashion as they are released. A Phase 1/2 study of the same vaccine candidates (BNT162-01), conducted in Germany by BioNTech in adults 18 to 55 years of age, is planned to start in April 2020. Study C4591001 is designed to complement and expand upon the German study and confirm the optimal vaccine candidate(s) (BNT162a1, BNT162b1, BNT162b2, or BNT162c2), dose level(s), number of doses, and schedule of administration.

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, in sentinel cohorts from Stage 1, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: ***Stage 1 Sentinel Cohorts:*** 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts:*** 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 3 Cohort(s):*** 1, 12, and 24 months after Dose 2	

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emea.europa.eu

Objectives	Estimands	Endpoints
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 serum neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from rise from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2-S1–specific binding antibody levels and RBD-specific binding antibody levels
To evaluate the efficacy of prophylactic BNT162 vaccines against confirmed COVID-19	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 serum neutralizing titers to the geometric mean of SARS-CoV-2–specific binding antibody levels at each time point In participants complying with the key protocol criteria (evaluable participants) following receipt of the last dose of study intervention: 100 × (1 – illness rate ratio) [ratio of active vaccine to placebo]	• SARS-CoV-2 serum neutralizing titers • SARS-CoV-2-S1–specific binding antibody levels • SARS-CoV-2 RBD–specific binding antibody levels COVID-19 incidence per 1000 person-years of follow-up
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
To describe the relationship between SARS-CoV-2 serological parameters and: • NAAT-confirmed COVID-19 • Symptomatic SARS-CoV-2 infection • Asymptomatic SARS-CoV-2 infection		Nonvaccine antigen SARS-CoV-2 antibody levels

Overall Design

This is a Phase 1/2, randomized, placebo-controlled, observer-blind, dose-finding, and vaccine candidate–selection study in healthy adults.

The study will evaluate the safety, tolerability, immunogenicity, and potential efficacy of up to 4 different SARS-CoV-2 RNA vaccine candidates against COVID-19:

- As a 2-dose (separated by 21 or 60 days) or single-dose schedule

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- At up to 3 different dose levels

- In 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age])

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study consists of 3 stages. Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3: a final candidate/dose large-scale stage. These stages, and the progression between them, are detailed in the schema (Section 1.2).

Number of Participants

Each group in Stage 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this stage, assuming 2 dose levels are selected following the initial dose escalation, up to 56 potential groups are foreseen; if all groups are fully enrolled, this corresponds to a total of 840 participants.

Each group in Stage 2 will comprise 225 participants (180 receiving active vaccine and 45 receiving placebo). The total number of participants to be enrolled in this stage depends on the number of groups to be pursued.

The vaccine candidate/dose level selected for Stage 3 will comprise 3000 participants. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study may evaluate single-dose and 2-dose (separated by 21 or 60 days) schedules of 3 different dose levels of 4 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age]):

- BNT162a1 (RNA-LNP vaccine utilizing uRNA and encoding the RBD): 0.1 µg, 0.3 µg, 1 µg

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 30 µg, 100 µg

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 30 µg, 100 µg

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- BNT162c2 (BNT162 RNA-LNP vaccine utilizing saRNA and encoding the RBD): 0.1 µg, 0.3 µg, 1 µg

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Stage 1 and Stage 2 dosing arms that are not evaluated in Stage 3.

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The study sample size for the first 2 stages of the study is not based on any statistical hypothesis testing. For the third stage, with assumptions of a true vaccine efficacy (VE) of 70%, 53 cases of COVID-19 will provide 90% power to conclude true VE >20%. This would be achieved with 3000 participants per group, based on the assumption of a 1.7% incidence rate in the placebo group, and 20% of the participants being nonevaluable.

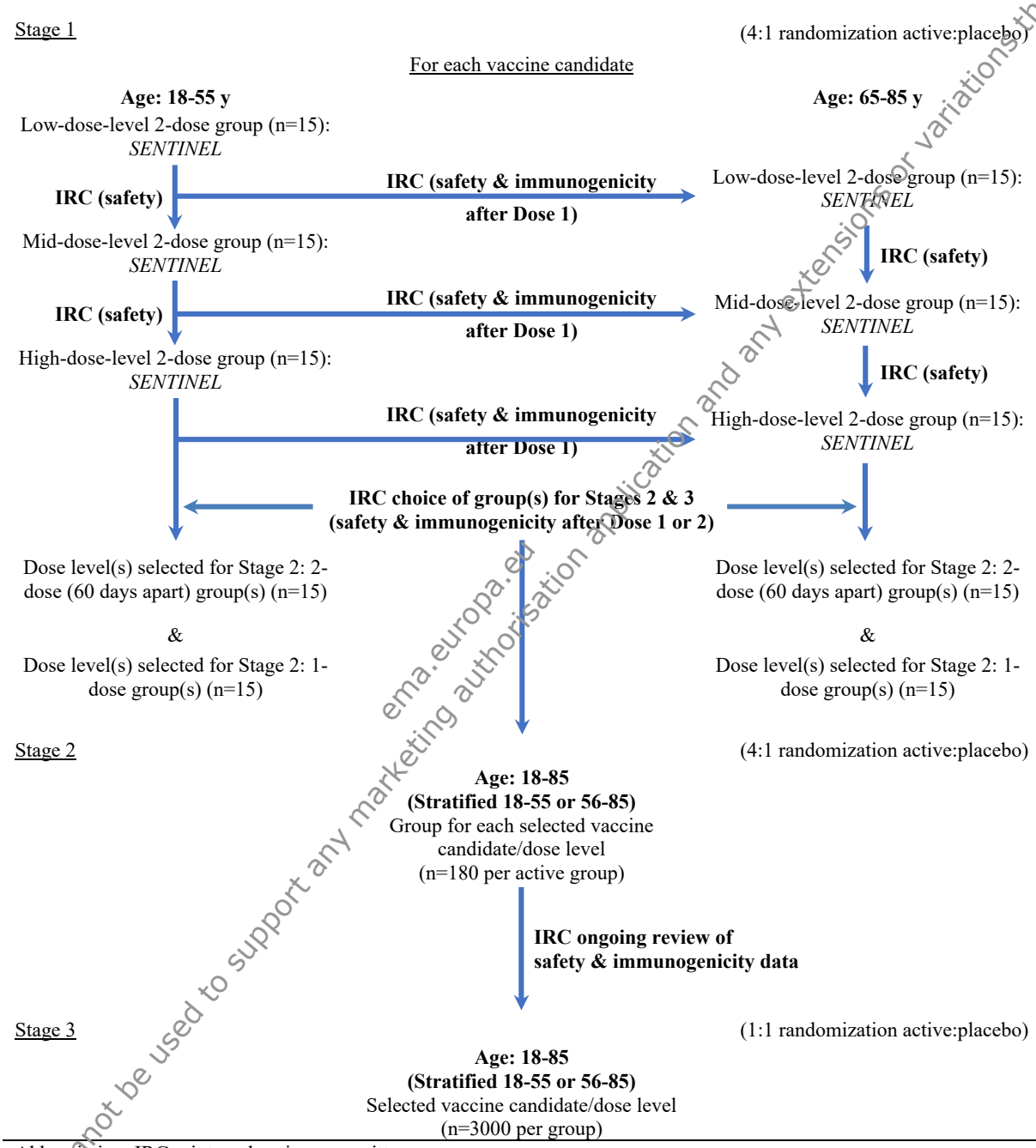
The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, abnormal hematology and chemistry laboratory parameters (sentinel cohorts only), and AEs and SAEs, for each vaccine group. A 3-tier approach will be used to summarize AEs.

The secondary immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 serum neutralizing titers, SARS-CoV-2-S1–specific binding antibody levels, and RBD-specific binding antibody levels at the various time points.

For the secondary efficacy objective, VE is defined as VE = 100 × (1 – IRR), where IRR is the illness rate ratio, the calculated ratio of COVID-19 incidence in the active vaccine group to the incidence in the placebo group. The null hypothesis (VE ≤ 20%) will be rejected if the lower bound of the 95% CI for VE is >20%; no interim analysis of VE is planned.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

1.2. Schema



Abbreviation: IRC = internal review committee.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Stage 1 Sentinel Cohorts

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[a]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[b]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL		~50 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[c]		X			X								
Provide participant with 7-day e-diary, thermometer, and measuring device		X			X								
Review e-diary data (daily review is optimal during the active diary period)		◄	———	►	◄	——►							
Review ongoing e-diary symptoms and obtain stop dates					X		X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collect e-diary or assist the participant to delete application							X						
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
b. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
c. The first 5 participants in in each sentinel group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

1.3.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 7 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	1	2	3	4	5	6	7	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**12 to 16 Days After Visit 2**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X								
Assign participant number	X								
Obtain demography and medical history data	X								
Perform physical examination	X								
Measure vital signs	X								
Perform urine pregnancy test (if appropriate)	X	X							
Collect nonstudy vaccine information	X	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X	X
Confirm eligibility	X	X							
Measure temperature (body)	X	X							
Review temporary delay criteria	X	X							
Confirm use of contraceptives (if appropriate)	X	X	X	X					
Obtain randomization number and study intervention allocation	X								

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	1	2	3	4	5	6	7	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**12 to 16 Days After Visit 2**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL		~50 mL
Obtain nasal (midturbinate) swab	X	X						X	
Administer study intervention	X	X							
Assess acute reactions for at least 30 minutes after study intervention administration	X	X							
Provide participant with 7-day e-diary, thermometer, and measuring device	X	X							
Review e-diary data (daily review is optimal during the active diary period)	←→	←→							
Review ongoing e-diary symptoms and obtain stop dates		X	X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application			X						
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)								X	X

Abbreviation: e-diary = electronic diary.

a. The window for Visit 2 is dependent on the dosing schedule for the assigned group.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Stage 3 Cohort(s)

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	1	2	3	4	5	6	Unplanned 1	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Safety Telephone Contact**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform physical examination	X							
Measure vital signs	X							
Perform urine pregnancy test (if appropriate)	X	X						
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Measure temperature (body)	X	X						
Review temporary delay criteria	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Obtain randomization number and study intervention allocation	X							
Collect blood sample for immunogenicity assessment	~50 mL		~50 mL		~50 mL	~50 mL		~50 mL
Obtain nasal (midturbinate) swab	X	X					X	

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Safety Telephone Contact**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Administer study intervention	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Provide participant with 7-day e-diary, thermometer, and measuring device	X	X						
Review e-diary data (daily review is optimal during the active diary period)	←→	←→						
Review ongoing e-diary symptoms and obtain stop dates		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application			X					
Telephone contact				X				
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviation: e-diary = electronic diary.

a. The window for Visit 2 is dependent on the dosing schedule(s) selected for the Stage 3.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy adults.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, immunogenicity, and potential efficacy of 4 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19 in healthy adults. There are currently no vaccines to prevent infection with SARS-CoV-2 or antiviral drugs to treat COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with

traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Four SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines utilizing different RNA formats will be evaluated in this study. Each vaccine candidate is based on 1 of 3 RNA platforms: unmodified messenger RNA (uRNA, BNT162a), nucleoside-modified messenger RNA (modRNA, BNT162b), or self-amplifying messenger RNA (saRNA, BNT162c). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor binding domain (RBD) (version 5). The 4 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

- **BNT162a1** (variant RBL063.3): non–nucleoside-modified uridine-containing messenger RNA (uRNA) with high intrinsic adjuvanticity, encoding the RBD.
- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.
- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above but encoding P2 S.
- **BNT162c2** (variant RBS004.2): self-amplifying messenger RNA (saRNA) encoding the P2 S, in which higher amounts of protein per injected RNA template can be produced.

2.2.1. Clinical Overview

BNT162 vaccines have not been administered to humans before and thus there are no previous clinical data with these specific vaccines. However, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines are expected to have a favorable safety profile with mild, localized, and transient effects.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there are currently no data available from clinical trials on the use of BNT162 vaccines in humans, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, support a favorable risk/benefit profile. Anticipated AEs after vaccination are expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates support initiation of this Phase 1/2 clinical study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the investigator's brochure (IB), which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The study design includes the use of sentinel cohorts and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of an e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place for sentinel cohorts. The first 5 sentinel-cohort participants in each group will be observed for 4 hours after vaccination to assess any immediate AEs.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The study design includes the use of sentinel cohorts and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC and DMC will also review safety data throughout the study. Stopping rules are also in place for sentinel cohorts. The first 5 sentinel cohort participants in each group will be observed for 4 hours after vaccination to assess any immediate AEs.
Potential for COVID-19 disease enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	The study excludes participants with likely previous or current COVID-19. All participants are followed for SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 serum neutralizing titers, and COVID-19 illness, including markers of severity.
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e19376358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of a potentially efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic and antibody testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, in sentinel cohorts from Stage 1, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: ***Stage 1 Sentinel Cohorts:*** 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts:*** 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 3 Cohort(s):*** 1, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 serum neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2-S1–specific binding antibody levels and RBD-specific binding antibody levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 serum neutralizing titers to the geometric mean of SARS-CoV-2–specific binding antibody levels at each time point	• SARS-CoV-2 serum neutralizing titers • SARS-CoV-2-S1–specific binding antibody levels • SARS-CoV-2 RBD–specific binding antibody levels
To evaluate the efficacy of prophylactic BNT162 vaccines against confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants) following receipt of the last dose of study intervention: 100 × (1 – illness rate ratio) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Objectives	Estimands	Endpoints
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
To describe the relationship between SARS-CoV-2 serological parameters and: • NAAT-confirmed COVID-19 • Symptomatic SARS-CoV-2 infection • Asymptomatic SARS-CoV-2 infection		Nonvaccine antigen SARS-CoV-2 antibody levels

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1/2, randomized, placebo-controlled, observer-blind, dose-finding, and vaccine candidate–selection study in healthy adults.

The study will evaluate the safety, tolerability, immunogenicity, and potential efficacy of up to 4 different SARS-CoV-2 RNA vaccine candidates against COVID-19:

- As a 2-dose (separated by 21 or 60 days) or single-dose schedule
- At up to 3 different dose levels
- In 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age])

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study consists of 3 stages. Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3; a final candidate/dose large-scale stage. These stages, and the progression between them, are detailed in the schema (Section 1.2).

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Stage 1 and Stage 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

4.1.1. Stage 1

Each group (vaccine candidate/dose level/age group/number of doses) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo. On Day 22, those in 2-dose groups will receive the same vaccine they received on Day 1; for those in single-dose groups, all will receive placebo. Full details of all potential groups in Stage 1 may be found in Table 1.

For each vaccine candidate/dose level/age group, the 15 participants randomized into each 2-dose group will comprise a sentinel cohort, to which the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment:
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level:
  - Escalation between dose levels in the 18- to 55-year age cohort will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
  - Escalation between dose levels in the 65- to 85-year age cohort will be based on IRC review of:
    - At least 4-week post–Dose 1 safety data for the corresponding dose level in the 18- to 55-year age cohort in this study and/or the BioNTech study conducted in Germany (BNT162-01) and
    - At least 24-hour post–Dose 1 safety data in this study for the prior dose level in the 65- to 85-year age cohort
  - Note that, for candidates based upon the same RNA platform (eg, BNT162b1 and BNT162b2), the stated observation periods may be shortened to 24 hours for the second candidate studied, if the safety profile of the first candidate studied was deemed acceptable at the same dose level by the IRC

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Groups of participants 65 to 85 years of age will not be started until safety and immunogenicity data for the same RNA platform/dose level have been deemed acceptable in the 18- to 55-year age cohort by the IRC.

Once the IRC has selected a vaccine candidate/dose level to proceed into Stage 2, for each age cohort, 2 additional groups will be enrolled into Stage 1 for that vaccine candidate/dose level:

- A 2-dose group, with the 2 doses administered 60 days apart rather than 21
- A 1-dose group

In this stage, assuming 2 dose levels are selected following the initial dose escalation, up to 56 potential groups are foreseen; if all groups are fully enrolled, this corresponds to a total of 840 participants.

4.1.2. Stage 2

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 or more groups (vaccine candidate/dose level) may be selected to proceed into Stage 2. Participants in this stage will be 18 to 85 years of age, stratified equally: 18 to 55 or 56 to 85 years. Commencement of each age stratum will be dependent upon satisfactory safety and immunogenicity data from the 18- to 55-year and 65- to 85-year groups from Stage 1, respectively. It is therefore possible that the 2 age strata may not start concurrently.

In each group selected for Stage 2, it is intended that 225 participants will be randomized in a 4:1 ratio to receive active vaccine (180 participants) or placebo (45 participants).

4.1.3. Stage 3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 group may be selected to proceed into Stage 3. Participants in this stage will be 18 to 85 years of age, stratified equally: 18 to 55 years or 56 to 85 years. As in Stage 2, it is possible that the 2 age strata may not start concurrently.

The vaccine candidate/dose level selected for Stage 3 will comprise 3000 participants. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Stage 1 and Stage 2 dosing arms that are not evaluated in Stage 3.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences respiratory symptoms, as

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data are not currently available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting doses of 3 µg (for BNT162a1 and BNT162c2) and 10 µg (for BNT162b1 and BNT162b2) in this study were based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components (uRNA, modRNA, saRNA), with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 1: preliminary experience in the BioNTech study conducted in Germany (BNT162-01), following vaccination of 6 participants with 3 µg of BNT162a1, demonstrated an undesirable level of systemic reactogenicity. Therefore, potential dose levels for BNT162a1 and BNT162c2 (which are both based upon unmodified RNA) dependent upon further data from the BNT162-01 study, are each reduced 30-fold to 0.1 µg, 0.3 µg, and 1 µg.

Taken together, the planned starting doses in this study in healthy participants are considered to be safe, but still sufficient to induce an antiviral immune response.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Stages 1 and 2 in groups that do not proceed to Stage 3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

The end of the study is defined as the date of last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, 65 and 85 years, inclusive, or 18 and 85 years, inclusive, at randomization (dependent upon study stage).

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.

Informed Consent:

4. Capable of giving personal signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. **Stages 1 and 2 only:** Previous clinical or microbiological diagnosis of COVID-19.

6. **Sentinel participants in Stage 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - Chronic liver disease
    - Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
    - Resident in a long-term facility
    - BMI >30 kg/m^2
    - Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Sentinel participants in Stage 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for sentinel participants in Stage 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Sentinel participants in Stage 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Sentinel participants in Stage 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.au

19. **Sentinel participants in Stage 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Sentinel participants in Stage 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Sentinel participants in Stage 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
   - New or increased cough;
   - New or increased shortness of breath;
   - New or increased sore throat;
   - New or increased wheezing;
   - New or increased sputum production;
   - New or increased nasal congestion;
   - New or increased nasal discharge;
   - Loss of taste/smell.
2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.
3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.
4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study may evaluate 2-dose (separated by 21 or 60 days) and single-dose schedules of 3 different dose levels of 4 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age]). These 4 investigational RNA

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

vaccine candidates, with the addition of saline placebo, are the 5 potential study interventions that may be administered to a study participant:

- BNT162a1 (RNA-LNP vaccine utilizing uRNA and encoding the RBD): 0.1 µg, 0.3 µg, 1 µg
- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 30 µg, 100 µg
- BNT162c2 (BNT162 RNA-LNP vaccine utilizing saRNA and encoding the RBD): 0.1 µg, 0.3 µg, 1 µg
- Normal saline (0.9% sodium chloride solution for injection)

A list of all potential groups in the Stage 1 are shown in Table 1. Each of these groups may or may not progress to the later stages of the study.

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
2-Dose Groups (Sentinel Cohorts)			**Day 1**			**Day 22**		
a-0.1-2-Y (Sentinel) [uRNA 0.1 µg (2 doses)]	15	18 to 55	BNT162a1 Placebo	0.1 µg	(n=12) (n=3)	BNT162a1 Placebo	0.1 µg	(n=12) (n=3)
a-0.3-2-Y (Sentinel) [uRNA 0.3 µg (2 doses)]	15	18 to 55	BNT162a1 Placebo	0.3 µg	(n=12) (n=3)	BNT162a1 Placebo	0.3 µg	(n=12) (n=3)
a-1-2-Y (Sentinel) [uRNA 1 µg (2 doses)]	15	18 to 55	BNT162a1 Placebo	1 µg	(n=12) (n=3)	BNT162a1 Placebo	1 µg	(n=12) (n=3)
b1-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	10 µg	(n=12) (n=3)	BNT162b1 Placebo	10 µg	(n=12) (n=3)
b1-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	30 µg	(n=12) (n=3)	BNT162b1 Placebo	30 µg	(n=12) (n=3)
b1-100-2-Y (Sentinel) [modRNA 100 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	100 µg	(n=12) (n=3)	BNT162b1 Placebo	100 µg	(n=12) (n=3)
b2-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	10 µg	(n=12) (n=3)	BNT162b2 Placebo	10 µg	(n=12) (n=3)
b2-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	30 µg	(n=12) (n=3)	BNT162b2 Placebo	30 µg	(n=12) (n=3)
b2-100-2-Y (Sentinel) [modRNA 100 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	100 µg	(n=12) (n=3)	BNT162b2 Placebo	100 µg	(n=12) (n=3)

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
c-0.1-2-Y (Sentinel) [saRNA 0.1 µg (2 doses)]	15	18 to 55	BNT162c2 Placebo	0.1 µg	(n=12) (n=3)	BNT162c2 Placebo	0.1 µg	(n=12) (n=3)
c-0.3-2-Y (Sentinel) [saRNA 0.3 µg (2 doses)]	15	18 to 55	BNT162c2 Placebo	0.3 µg	(n=12) (n=3)	BNT162c2 Placebo	0.3 µg	(n=12) (n=3)
c-1-2-Y (Sentinel) [saRNA 1 µg (2 doses)]	15	18 to 55	BNT162c2 Placebo	1 µg	(n=12) (n=3)	BNT162c2 Placebo	1 µg	(n=12) (n=3)
a-0.1-2-O (Sentinel) [uRNA 0.1 µg (2 doses)]	15	65 to 85	BNT162a1 Placebo	0.1 µg	(n=12) (n=3)	BNT162a1 Placebo	0.1 µg	(n=12) (n=3)
a-0.3-2-O (Sentinel) [uRNA 0.3 µg (2 doses)]	15	65 to 85	BNT162a1 Placebo	0.3 µg	(n=12) (n=3)	BNT162a1 Placebo	0.3 µg	(n=12) (n=3)
a-1-2-O (Sentinel) [uRNA 1 µg (2 doses)]	15	65 to 85	BNT162a1 Placebo	1 µg	(n=12) (n=3)	BNT162a1 Placebo	1 µg	(n=12) (n=3)
b1-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	10 µg	(n=12) (n=3)	BNT162b1 Placebo	10 µg	(n=12) (n=3)
b1-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	30 µg	(n=12) (n=3)	BNT162b1 Placebo	30 µg	(n=12) (n=3)
b1-100-2-O (Sentinel) [modRNA 100 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	100 µg	(n=12) (n=3)	BNT162b1 Placebo	100 µg	(n=12) (n=3)
b2-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	10 µg	(n=12) (n=3)	BNT162b2 Placebo	10 µg	(n=12) (n=3)
b2-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	30 µg	(n=12) (n=3)	BNT162b2 Placebo	30 µg	(n=12) (n=3)
b2-100-2-O (Sentinel) [modRNA 100 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	100 µg	(n=12) (n=3)	BNT162b2 Placebo	100 µg	(n=12) (n=3)
c-0.1-2-O (Sentinel) [saRNA 0.1 µg (2 doses)]	15	65 to 85	BNT162c2 Placebo	0.1 µg	(n=12) (n=3)	BNT162c2 Placebo	0.1 µg	(n=12) (n=3)
c-0.3-2-O (Sentinel) [saRNA 0.3 µg (2 doses)]	15	65 to 85	BNT162c2 Placebo	0.3 µg	(n=12) (n=3)	BNT162c2 Placebo	0.3 µg	(n=12) (n=3)
c-1-2-O (Sentinel) [saRNA 1 µg (2 doses)]	15	65 to 85	BNT162c2 Placebo	1 µg	(n=12) (n=3)	BNT162c2 Placebo	1 µg	(n=12) (n=3)
Single-Dose Groups			**Day 1**			**Day 22**		
a-x-1-Y [uRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162a1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b1-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b2-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
c-x-1-Y	15	18 to 55	BNT162c2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)

This document is made available to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
[saRNA dose level(s) selected for Stage 2 (1 dose)]								
a-x-1-O [uRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162a1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b1-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b2-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
c-x-1-O [saRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162c2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
2-Dose Groups (Longer Schedule)			**Day 1**			**Day 61**		
a-x-2L-Y [uRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162a1 Placebo	TBD	(n=12) (n=3)	BNT162a1 Placebo	TBD	(n=12) (n=3)
b1-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b1 Placebo	TBD	(n=12) (n=3)	BNT162b1 Placebo	TBD	(n=12) (n=3)
b2-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b2 Placebo	TBD	(n=12) (n=3)	BNT162b2 Placebo	TBD	(n=12) (n=3)
c-x-2L-Y [saRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162c2 Placebo	TBD	(n=12) (n=3)	BNT162c2 Placebo	TBD	(n=12) (n=3)
a-x-2L-O [uRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162a1 Placebo	TBD	(n=12) (n=3)	BNT162a1 Placebo	TBD	(n=12) (n=3)
b1-x-2L-O [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162b1 Placebo	TBD	(n=12) (n=3)	BNT162b1 Placebo	TBD	(n=12) (n=3)
b2-x-2L-O [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162b2 Placebo	TBD	(n=12) (n=3)	BNT162b2 Placebo	TBD	(n=12) (n=3)
c-x-2L-O	15	65 to 85	BNT162c2 Placebo	TBD	(n=12) (n=3)	BNT162c2 Placebo	TBD	(n=12) (n=3)

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document can not be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1	Dose 2
[saRNA dose level(s) selected for Stage 2 (2 doses)]				

Abbreviations: modRNA = nucleoside-modified messenger ribonucleic acid; saRNA = self-amplifying messenger ribonucleic acid; TBD = to be determined; uRNA = uridine-containing messenger ribonucleic acid.

6.1. Study Intervention(s) Administered

Intervention Name	BNT162a1 (BNT 162 RNA-LNP vaccine utilizing uRNA)	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162c2 (BNT162 RNA-LNP vaccine utilizing saRNA	Saline placebo
Type	Vaccine	Vaccine	Vaccine	Vaccine	Placebo
Dose Formulation	uRNA	modRNA	modRNA	saRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	0.1-, 0.3-, 1-µg	10-, 30-, 100-µg	10-, 30-, 100-µg	0.1-, 0.3-, 1-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

6.1.1. Administration

Participants will receive 1 dose (0.5 mL) of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Stage 1 sentinel cohort participants, Visits 1 and 2 for all other participants) in accordance with the study's SoA.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Stage 1 and in Stage 2. Sponsor staff will be blinded to study intervention allocation in Stage 3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study.

Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate). Unblinded clinician(s) who are not direct members of the study team will review unblinded protocol deviations.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Stage 1 sentinel cohorts, Visit 5 for Stage 1 nonsentinel cohorts and Stage 2 participants, and Visit 4 for Stage 3 participants).

- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

- In addition, for participants enrolled in the Stage 1 sentinel cohorts, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 for Stage 1 sentinel cohorts, Visit 4 for Stage 1 nonsentinel cohorts and Stage 2 participants, and Visit 3 for Stage 3 participants).

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Stage 1 sentinel cohorts.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Stage 1 sentinel cohorts – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

Individual participant dose modifications will not be made in this study.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria).

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 530 mL for participants in the Stage 1 sentinel cohorts; 350 mL for participants in the Stage 1 nonsentinel cohorts and Stage 2 participants; and 200 mL for Stage 3 participants. Additionally, 50 mL of blood will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, a telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. Four definitions of potential SARS-CoV-2–related cases will be considered:

- Centrally confirmed COVID-19: presence of at least 1 symptom described in Section 8.13 and SARS-CoV-2 NAAT positive at central laboratory

- Locally confirmed COVID-19: presence of at least 1 symptom described in Section 8.13 and investigator-confirmed SARS-CoV-2 NAAT positive at a local testing facility

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Centrally confirmed symptomatic seroconversion to SARS-CoV-2 (exploratory): presence of at least 1 symptom described in Section 8.13 and a positive nonvaccine antigen SARS-CoV-2 antibody result in a participant whose most recent prior nonvaccine antigen SARS-CoV-2 antibody result was negative

- Centrally confirmed asymptomatic seroconversion to SARS-CoV-2 (exploratory): positive nonvaccine antigen SARS-CoV-2 antibody result in a participant with a prior nonvaccine antigen SARS-CoV-2 antibody result was negative

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 serum neutralization assay

- SARS-CoV-2-S1–specific IgG direct Luminex immunoassay

- SARS-CoV-2 RBD–specific IgG direct Luminex immunoassay

- Nonvaccine antigen (NVA) Ig direct Luminex immunoassay. The NVA will include a SARS-CoV-2 target antigen that is not derived from the S glycoprotein, most likely an antigen derived from the SARS-CoV-2 nucleoprotein.

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Stage 1 sentinel cohorts (see Section 8.11.1.1) to determine eligibility.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Stage 1 sentinel group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2.

8.2.1. Clinical Safety Laboratory Assessments (Sentinel-Cohort Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

8.2.2. Electronic Diary

Participants will be required to complete an e-diary through an application installed on a provisioned device or on the participant's own personal device. The participant will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. The e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

8.2.2.2. Local Reactions

During the e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary. If a local reaction persists beyond the end of the e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 2. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

If a Grade 3 local reaction is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 3.

If a Grade 3 systemic event is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Table 3. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the e-diary in the evening daily during the e-diary reporting period. It will also be collected at any time during the e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 4.

If a fever of ≥39.0°C (102.1°F) is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Table 4. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Stopping Rules

The following stopping rules are in place for all Stage 1 sentinel-cohort participants, based on review of AE data and e-diary reactogenicity data. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during the Stage 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. E-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

BNT162 RNA platforms (ie, a, b, and c) will be evaluated for contribution to stopping rules individually; vaccine candidate dose levels within a platform and age groups will contribute

This document cannot be used to support any marketing authorisation application on ema.europa.eu and any extensions or variations thereof

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19 disease.

8.2.3.1. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC and DMC have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 Disease

As this is a sponsor open-label study during Stages 1 and 2, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment.

Participants in all stages of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13). All NAAT-confirmed cases will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6). In addition, instances of symptomatic and asymptomatic seroconversion to SARS-CoV-2 (see Section 8.1) will be reviewed.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater severity, compared to available information at the time of

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review. Since the DMC is able to review unblinded information, it will also be able to compare cases in active vaccine and placebo recipients in Stage 3 (when sponsor staff will be blinded).

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Stage 1 sentinel-cohort participants, Visit 4 for Stage 1 nonsentinel participants and Stage 2 participants, and Visit 3 for Stage 3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Stage 1 sentinel-

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

cohort participants, Visit 5 for Stage 1 nonsentinel cohort participants and Stage 2 participants, and Visit 4 for Stage 3 participants).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccines SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccines SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccines SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are recorded on the CRF. AEs and SAEs that begin after obtaining informed consent but before the start of study intervention will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section. AEs and SAEs that begin after the start of study intervention are recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccines SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccines SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccines SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccines SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

8.3.6. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccines SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

8.11.1. Stage 1 Sentinel Cohorts

8.11.1.1. Screening: (0 to 14 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.5.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.

- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- The first 5 participants vaccinated in each Stage 1 sentinel group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Explain the e-diary technologies available for this study, and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

  Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy (see Section 7.1).

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (≥20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study, and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)

The window for Visit 2 is dependent on the dosing schedule for the assigned group.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy (see Section 7.1).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 2-Week Follow-up Visit: (12 to 16 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.11.2.4. Visit 4 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.5. Visit 5 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.7. Visit 7 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.3. Stage 3 Cohort(s)

8.11.3.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study, and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.3.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)

The window for Visit 2 is dependent on the dosing schedule(s) selected for Stage 3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.3.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.3.4. Visit 4 – 6-Month Safety Telephone Contact: (154 to 168 Days After Visit 2)

- Contact the participant by telephone in order to obtain the following information.
- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.3.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.3.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Disease Surveillance (All Participants)

If a participant experiences any of the following, he or she is instructed to contact the site immediately, and if confirmed, participate in a telehealth visit as soon as possible, optimally within 3 days of symptom onset. Note that this does not substitute for a participant's routine medical care. Therefore participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- New or increased sore throat;
- New or increased wheezing;
- New or increased sputum production;

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- New or increased nasal congestion;
- New or increased nasal discharge;
- Loss of taste/smell.

8.13.1. Potential COVID-19 Illness Telehealth Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This telehealth visit is expected to involve the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several telehealth contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory. The result from this swab will be provided to the site once it is available, but this will not be in real time, and cannot be relied upon to direct clinical care. Therefore, the participant should be encouraged to seek care, if appropriate, from his or her usual provider.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
  - Symptoms
  - Clinical diagnosis
  - Local laboratory COVID-19 test result
  - Full blood count
  - C-reactive protein
  - Number and type of any healthcare contact; duration of hospitalization and intensive care unit stay
  - Need for oxygen therapy
  - Need for ventilation

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

At the end of Stage 3, the vaccine efficacy (VE) will be evaluated. VE is defined as VE = 100 × (1 – IRR), where IRR is the illness rate ratio, the calculated ratio of the COVID-19 illness rate in the active vaccine group to the incidence rate in the placebo group. The efficacy hypothesis is:

H_0: VE ≤20% vs H_a: VE >20%

where H_0 and H_a represent null hypothesis and alternative hypothesis. For participants with multiple illnesses, only the first COVID-19 confirmed case will contribute to the VE calculation in the hypothesis test.

The efficacy will be demonstrated if the null hypothesis VE ≤20% is rejected at the 0.025 significance level, that is, when the lower limit of the 2-sided 95% CI for VE is >20%, which is derived using the Clopper-Pearson method as described by Agresti.[9]

9.2. Sample Size Determination

The study sample size for the first 2 stages of the study is not based on any statistical hypothesis testing. Stage 1 will comprise 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; up to 56 potential groups are foreseen; if all groups are fully enrolled, assuming 2 dose levels are selected following the initial dose escalation, this corresponds to a total of 840 participants. Stage 2 will include 1 or more vaccine groups selected from Stage 1, and 225 participants will be randomized per selected vaccine candidate in a 4:1 ratio to receive active vaccine (180 participants) or placebo (45 participants).

For Stage 3, for the selected vaccine candidate/dose level, with assumptions of a true vaccine efficacy (VE) of 70%, 53 cases of COVID-19 will provide 90% power to conclude true VE >20%. This would be achieved with 3000 participants per group (1:1 randomization ratio), based on the assumption of a 1.7% incidence rate in the placebo group, and 20% of the participants being nonevaluable.

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=3000
0.10%	0.01	0.04	0.16	0.95
0.50%	0.06	0.20	0.59	>0.99
1.00%	0.11	0.36	0.84	>0.99
2.00%	0.22	0.60	0.97	>0.99
3.00%	0.31	0.75	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	All eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result 21 days after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other major protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other major protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Population	Description
Evaluable efficacy	All eligible randomized participants who receive vaccination(s) as randomized within the predefined window, have the efficacy measurement after the last dose of study intervention, and have no other major protocol deviations as determined by the clinician.
All-available efficacy	All eligible randomized participants who receive at least 1 vaccination and have the efficacy measurement at any time after Dose 1.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 serum neutralizing titers and SARS-CoV-2-S1–specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2-S1–specific binding antibody levels and RBD-specific binding antibody levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product (active/placebo) within each group before vaccination and at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 12, and 24 months after Dose 2 Geometric means and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on the t-distribution, and then exponentiating the results. **GMFRs of SARS-CoV-2 serum neutralizing titers and SARS-CoV-2-S1–specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2-S1–specific antibody levels and RBD-specific binding antibody levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and transformed back to the original scale. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Endpoint	Statistical Analysis Methods
	the logarithmically transformed assay results and transforming the limits back to the original scale. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 serum neutralizing titers and SARS-CoV-2-S1–specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2-S1–specific antibody levels and RBD-specific binding antibody levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 serum neutralizing titer to SARS-CoV-2-S1–specific antibody and SARS-CoV-2 RBD–specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2-S1–specific binding antibody levels and RBD-specific binding antibody levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 Cohort(s): 1, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 serum neutralizing titers and SARS-CoV-2-S1–specific antibody/SARS-CoV-2 RBD–specific binding antibody at each time

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 serum neutralizing titers minus SARS-CoV-2-S1–specific antibody for each participant) and transformed back to the original scale. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and transforming the limits back to the original scale. The same analysis methods will be applied to the immunogenicity endpoints in Stages 2 and 3. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Tertiary/ exploratory immunogenicity	**Correlation of an RT-PCR–confirmed COVID-19 infection and seropositivity/seroconversion measured by nonvaccine antigen SARS-CoV-2 antibody** If sufficient data are collected, percentages (and 2-sided 95% CIs) of participants with confirmed COVID-19 and nonvaccine antigen SARS-CoV-2 antibody levels after Dose 1 and after Dose 2 will be provided. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 serum neutralizing titers, SARS-CoV-2-S1–specific antibody, and RBD-specific binding antibody after Dose 1 and after Dose 2.

9.4.2. Efficacy Analyses

The statistical analysis of efficacy will be based on the evaluable efficacy population (primary analysis) and the all-available efficacy population as defined in Section 9.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Endpoint	Statistical Analysis Methods
Secondary efficacy	**Ratio of COVID-19 incidence per 1000 person-years of follow-up for the active vaccine group to the placebo group** Vaccine efficacy will be estimated by 100 × (1 – IRR), where IRR is the illness rate ratio, the calculated ratio of COVID-19 infection incidence per 1000 person-years follow-up in the active vaccine group to the corresponding incidence in the placebo group after 2 doses. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. For the primary analysis, missing efficacy data will not be imputed. A sensitivity analysis may be performed by imputing missing values; details will be provided in the SAP.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	• Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. • For Stage 1 sentinel cohorts, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. • AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Endpoint	Statistical Analysis Methods
	term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. • Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. • SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after last dose will be provided for each vaccine group. • The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	• Not applicable (N/A)
Exploratory	• N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 serum neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the SARS-CoV-2 S1–specific binding antibody level at the postvaccination time point to the corresponding antibody level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the SARS-CoV-2 RBD–specific binding antibody level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

9.5. Interim Analyses

No formal interim analysis is planned in this study. As this is a sponsor open-label study during Stages 1 and 2, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 3 weeks after Dose 2 for Stage 1.
- Complete safety and immunogenicity analysis approximately 3 weeks after Dose 2 for Stage 2.
- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3.
- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available at the end of the study.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC and a DMC. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC will include:

- Review of safety data to permit dose escalations
- Review of safety data in the case of a stopping rule being met
- Review of safety and immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate(s)/dose level(s) and schedule(s) to proceed into Stage 2. Data supporting the selection, including results for both binding antibody levels and serum neutralizing titers, and the ratio between them, will also be submitted to the FDA for review
  - Select vaccine candidate(s)/dose level(s) and schedule(s) to proceed into Stage 3. Data supporting the selection, including results for both binding antibody levels and

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

serum neutralizing titers, and the ratio between them, will also be submitted to the FDA for review

- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 6).

Table 6. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Female) change from baseline value – g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hemoglobin (Male) change from baseline value – g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Table 6. Laboratory Abnormality Grading Scale

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
Chemistry	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccines SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccines SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccines SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and EDP supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccines SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

This document cannot be used to support any marketing authorisation application or any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccines SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccines SAE Report Form
• Facsimile transmission of the Vaccines SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccines SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccines SAE Report Form pages within the designated reporting time frames.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

   - Oral;
   - Intravaginal;
   - Transdermal;
   - Injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - Oral;
   - Injectable.

8. Sexual abstinence:

   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use application
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Abbreviation	Term
HBc Ab	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
modRNA	nucleoside-modified messenger ribonucleic acid
N/A	not applicable
NAAT	nucleic acid amplification test
NVA	nonvaccine antigen
P2 S	SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Abbreviation	Term
PCR	polymerase chain reaction
PI	principal investigator
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal
uRNA	uridine-containing messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): therapeutic options. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Accessed: 12 Apr 2020.

4 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

5 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

6 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

7 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine. 2019;37(25):3326-34.

8 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

9 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

10 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol Amendment 1, Clean Version, May 13 2020
Document Title:	A PHASE 1/2, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO DESCRIBE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND POTENTIAL EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY ADULTS

Signed By:	Date(GMT)	Signing Capacity
PPD	14-May-2020 15:18:52	Business Line Approver
PPD	14-May-2020 15:30:33	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193765358\Approved\Approved On: 14-May-2020 15:30 (GMT)

A PHASE 1/2, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO DESCRIBE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND POTENTIAL EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY ADULTS

Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	N/A
Protocol Number:	C4591001
Phase:	1/2

Short Title: A Phase 1/2 Study to Describe the Safety, Tolerability, Immunogenicity, and Potential Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	15 April 2020	N/A

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 8
1. PROTOCOL SUMMARY 10
1.1. Synopsis 10
1.2. Schema 15
1.3. Schedule of Activities 16
1.3.1. Stage 1 Sentinel Cohorts 16
1.3.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts 20
1.3.3. Stage 3 Cohort(s) 22
2. INTRODUCTION 24
2.1. Study Rationale 24
2.2. Background 24
2.2.1. Clinical Overview 25
2.3. Benefit/Risk Assessment 25
2.3.1. Risk Assessment 27
2.3.2. Benefit Assessment 28
2.3.3. Overall Benefit/Risk Conclusion 28
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 28
4. STUDY DESIGN 30
4.1. Overall Design 30
4.1.1. Stage 1 30
4.1.2. Stage 2 31
4.1.3. Stage 3 32
4.2. Scientific Rationale for Study Design 32
4.3. Justification for Dose 32
4.4. End of Study Definition 33
5. STUDY POPULATION 33
5.1. Inclusion Criteria 33
5.2. Exclusion Criteria 34
5.3. Lifestyle Considerations 36
5.3.1. Contraception 36

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

5.4. Screen Failures 36
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration 37
6. STUDY INTERVENTION 37
6.1. Study Intervention(s) Administered 41
6.1.1. Administration 41
6.2. Preparation/Handling/Storage/Accountability 42
6.2.1. Preparation and Dispensing 43
6.3. Measures to Minimize Bias: Randomization and Blinding 43
6.3.1. Allocation to Study Intervention 43
6.3.2. Blinding of Site Personnel 43
6.3.3. Blinding of the Sponsor 44
6.3.4. Breaking the Blind 44
6.4. Study Intervention Compliance 44
6.5. Concomitant Therapy 44
6.5.1. Prohibited During the Study 45
6.5.2. Permitted During the Study 45
6.6. Dose Modification 46
6.7. Intervention After the End of the Study 46
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 46
7.1. Discontinuation of Study Intervention 46
7.2. Participant Discontinuation/Withdrawal From the Study 46
7.2.1. Withdrawal of Consent 47
7.3. Lost to Follow-up 47
8. STUDY ASSESSMENTS AND PROCEDURES 48
8.1. Efficacy and/or Immunogenicity Assessments 49
8.1.1. Biological Samples 50
8.2. Safety Assessments 50
8.2.1. Clinical Safety Laboratory Assessments (Sentinel-Cohort Participants Only) 50
8.2.2. Electronic Diary 51

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

8.2.2.1. Grading Scales....52
8.2.2.2. Local Reactions....52
8.2.2.3. Systemic Events....53
8.2.2.4. Fever....53
8.2.2.5. Antipyretic Medication....54
8.2.3. Stopping Rules....54
8.2.3.1. Randomization and Vaccination After a Stopping Rule Is Met....55
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 Disease....56
8.2.5. Pregnancy Testing....56
8.3. Adverse Events and Serious Adverse Events....56
8.3.1. Time Period and Frequency for Collecting AE and SAE Information....57
8.3.1.1. Reporting SAEs to Pfizer Safety....57
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF....57
8.3.2. Method of Detecting AEs and SAEs....58
8.3.3. Follow-up of AEs and SAEs....58
8.3.4. Regulatory Reporting Requirements for SAEs....58
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure....59
8.3.5.1. Exposure During Pregnancy....59
8.3.5.2. Exposure During Breastfeeding....60
8.3.5.3. Occupational Exposure....61
8.3.6. Medication Errors....61
8.4. Treatment of Overdose....62
8.5. Pharmacokinetics....62
8.6. Pharmacodynamics....63
8.7. Genetics....63
8.8. Biomarkers....63
8.9. Immunogenicity Assessments....63
8.10. Health Economics....63
8.11. Study Procedures....63

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

8.11.1. Stage 1 Sentinel Cohorts....63
8.11.1.1. Screening: (0 to 14 Days Before Visit 1)....63
8.11.1.2. Visit 1 – Vaccination 1: (Day 1)....64
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)....66
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)....67
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)....69
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)....71
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)....72
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)....73
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 4)....73
8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4)....74
8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4)....74
8.11.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts....75
8.11.2.1. Visit 1 – Vaccination 1: (Day 1)....75
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)....77
8.11.2.3. Visit 3 – 2-Week Follow-up Visit: (12 to 16 Days After Visit 2)....79
8.11.2.4. Visit 4 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 2)....79
8.11.2.5. Visit 5 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 2)....80
8.11.2.6. Visit 6 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)....80
8.11.2.7. Visit 7 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)....81
8.11.3. Stage 3 Cohort(s)....81
8.11.3.1. Visit 1 – Vaccination 1: (Day 1)....81

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

8.11.3.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1) 83
8.11.3.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2) 85
8.11.3.4. Visit 4 – 6-Month Safety Telephone Contact: (154 to 168 Days After Visit 2) 86
8.11.3.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2) 86
8.11.3.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2) 86
8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 87
8.13. COVID-19 Disease Surveillance (All Participants) 88
8.13.1. Potential COVID-19 Illness Telehealth Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 88
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit) 90
9. STATISTICAL CONSIDERATIONS 90
9.1. Estimands and Statistical Hypotheses 90
9.1.1. Estimands 90
9.1.2. Statistical Hypotheses 91
9.2. Sample Size Determination 91
9.3. Analysis Sets 92
9.4. Statistical Analyses 93
9.4.1. Immunogenicity Analyses 93
9.4.2. Efficacy Analyses 96
9.4.3. Safety Analyses 97
9.4.4. Other Analyses 98
9.5. Interim Analyses 99
9.5.1. Analysis Timing 99
9.6. Data Monitoring Committee or Other Independent Oversight Committee 99
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 101
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 101
10.1.1. Regulatory and Ethical Considerations 101

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 101
10.1.2. Informed Consent Process 102
10.1.3. Data Protection 103
10.1.4. Dissemination of Clinical Study Data 103
10.1.5. Data Quality Assurance 104
10.1.6. Source Documents 106
10.1.7. Study and Site Start and Closure 106
10.1.8. Sponsor's Qualified Medical Personnel 107
10.2. Appendix 2: Clinical Laboratory Tests 108
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 110
10.3.1. Definition of AE 110
10.3.2. Definition of SAE 111
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 113
10.3.4. Reporting of SAEs 116
10.4. Appendix 4: Contraceptive Guidance 117
10.4.1. Male Participant Reproductive Inclusion Criteria 117
10.4.2. Female Participant Reproductive Inclusion Criteria 117
10.4.3. Woman of Childbearing Potential 117
10.4.4. Contraception Methods 118
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 120
10.6. Appendix 6: Abbreviations 122
11. REFERENCES 125

LIST OF TABLES

Table 1. Potential Groups in Stage 1 38
Table 2. Local Reaction Grading Scale 52
Table 3. Systemic Event Grading Scale 53
Table 4. Scale for Fever 54
Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 92

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Table 6. Laboratory Abnormality Grading Scale 108

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2 Study to Describe the Safety, Tolerability, Immunogenicity, and Potential Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no vaccines to prevent infection with SARS-CoV-2 or antiviral drugs to treat COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on 1 of 3 RNA platforms: unmodified messenger RNA (uRNA), nucleoside-modified messenger RNA (modRNA), or self-amplifying messenger RNA (saRNA). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 4 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

BNT162a1 (variant RBL063.3): a uRNA encoding the RBD;

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S;

BNT162c2 (variant RBP020.3): an saRNA encoding the RBD.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and potential efficacy of these 4 prophylactic BNT162 vaccines against COVID-19.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

It is expected that the various candidate vaccines may not all be available from the start of the study, in which case they will be rolled into the study in a consecutive fashion as they are released. A Phase 1/2 study of the same vaccine candidates (BNT162-01), conducted in Germany by BioNTech in adults 18 to 55 years of age, is planned to start in April 2020. Study C4591001 is designed to complement and expand upon the German study and confirm the optimal vaccine candidate(s) (BNT162a1, BNT162b1, BNT162b2, or BNT162c2), dose level(s), number of doses, and schedule of administration.

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, in sentinel cohorts from Stage 1, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: ***Stage 1 Sentinel Cohorts:*** 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts:*** 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 3 Cohort(s):*** 1, 12, and 24 months after Dose 2	

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Objectives	Estimands	Endpoints
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2–specific WT serum neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from rise from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2–spike protein–specific binding antibody levels and RBD-specific binding antibody levels
To evaluate the efficacy of prophylactic BNT162 vaccines against confirmed COVID-19	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2–specific WT serum neutralizing titers to the geometric mean of SARS-CoV-2–specific binding antibody levels at each time point In participants complying with the key protocol criteria (evaluable participants) following receipt of the last dose of study intervention: 100 × (1 – infection rate ratio) [ratio of active vaccine to placebo]	• SARS-CoV-2–specific WT serum neutralizing titers • SARS-CoV-2-spike protein–specific binding antibody levels • SARS-CoV-2 RBD–specific binding antibody levels COVID-19 incidence per 1000 person-years of follow-up
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
To describe the relationship between SARS-CoV-2 serological parameters and: • NAAT-confirmed COVID-19 • Symptomatic SARS-CoV-2 infection • Asymptomatic SARS-CoV-2 infection		Nonvaccine antigen SARS-CoV-2 antibody levels

Overall Design

This is a Phase 1/2, randomized, placebo-controlled, observer-blind, dose-finding, and vaccine candidate–selection study in healthy adults.

The study will evaluate the safety, tolerability, immunogenicity, and potential efficacy of up to 4 different SARS-CoV-2 RNA vaccine candidates against COVID-19:

- As a 2-dose (separated by 21 or 60 days) or single-dose schedule

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- At up to 3 different dose levels

- In 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age])

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study consists of 3 stages. Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3: a final candidate/dose large-scale stage. These stages, and the progression between them, are detailed in the schema (Section 1.2).

Number of Participants

Each group in Stage 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this stage, assuming 2 dose levels are selected following the initial dose escalation, up to 56 potential groups are foreseen; if all groups are fully enrolled, this corresponds to a total of 840 participants.

Each group in Stage 2 will comprise 225 participants (180 receiving active vaccine and 45 receiving placebo). The total number of participants to be enrolled in this stage depends on the number of groups to be pursued.

The vaccine candidate/dose level selected for Stage 3 will comprise 3000 participants. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study may evaluate single-dose and 2-dose (separated by 21 or 60 days) schedules of 3 different dose levels of 4 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age]):

- BNT162a1 (RNA-LNP vaccine utilizing uRNA and encoding the RBD): 3 µg, 10 µg, 30 µg

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 30 µg, 100 µg

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 30 µg, 100 µg

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- BNT162c2 (BNT162 RNA-LNP vaccine utilizing saRNA and encoding the RBD): 3 µg, 10 µg, 30 µg

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Stage 1 and Stage 2 dosing arms that are not evaluated in Stage 3.

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The study sample size for the first 2 stages of the study is not based on any statistical hypothesis testing. For the third stage, with assumptions of a true vaccine efficacy (VE) of 70%, 53 cases of COVID-19 will provide 90% power to conclude true VE >20%. This would be achieved with 3000 participants per group, based on the assumption of a 1.7% incidence rate in the placebo group, and 20% of the participants being nonevaluable.

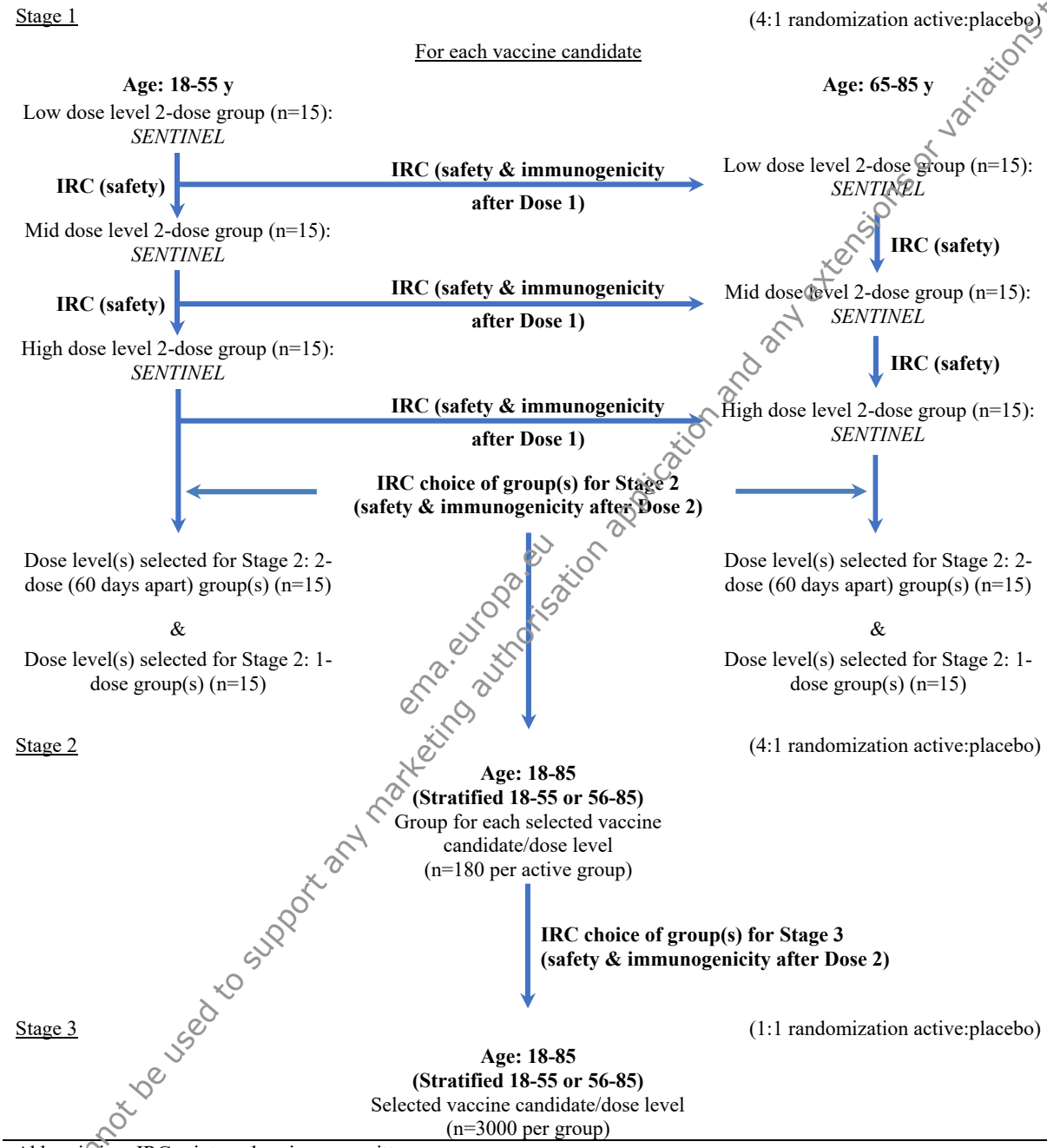
The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, abnormal hematology and chemistry laboratory parameters (sentinel cohorts only), and AEs and SAEs, for each vaccine group. A 3-tier approach will be used to summarize AEs.

The secondary immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2–specific WT serum neutralizing titers, SARS-CoV-2-spike protein–specific binding antibody levels, and RBD-specific binding levels at the various time points.

For the secondary efficacy objective, VE is defined as VE = 100 × (1 – IRR), where IRR is the infection rate ratio, the calculated ratio of COVID-19 incidence in the active vaccine group to the incidence in the placebo group. The null hypothesis (VE ≤ 20%) will be rejected if the lower bound of the 95% CI for VE is >20%; no interim analysis of VE is planned.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

1.2. Schema



Abbreviation: IRC = internal review committee.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Stage 1 Sentinel Cohorts

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[a]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[b]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL		~50 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[c]		X			X								
Provide participant with 7-day e-diary, thermometer, and measuring device		X			X								
Review e-diary data (daily review is optimal during the active diary period)		◄	———	►	◄	———	►						
Review ongoing e-diary symptoms and obtain stop dates					X		X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collect e-diary or assist the participant to delete application							X						
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
b. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
c. The first 5 participants in in each sentinel group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 7 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	1	2	3	4	5	6	7	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**12 to 16 Days After Visit 2**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X								
Assign participant number	X								
Obtain demography and medical history data	X								
Perform physical examination	X								
Measure vital signs	X								
Perform urine pregnancy test (if appropriate)	X	X							
Collect nonstudy vaccine information	X	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X	X
Confirm eligibility	X	X							
Measure temperature (body)	X	X							
Review temporary delay criteria	X	X							
Confirm use of contraceptives (if appropriate)	X	X	X	X					
Obtain randomization number and study intervention allocation	X								

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Visit Number	1	2	3	4	5	6	7	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**12 to 16 Days After Visit 2**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL		~50 mL
Obtain nasal (midturbinate) swab	X	X						X	
Administer study intervention	X	X							
Assess acute reactions for at least 30 minutes after study intervention administration	X	X							
Provide participant with 7-day e-diary, thermometer, and measuring device	X	X							
Review e-diary data (daily review is optimal during the active diary period)	←→	←→							
Review ongoing e-diary symptoms and obtain stop dates		X	X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application			X						
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)								X	X

Abbreviation: e-diary = electronic diary.

a. The window for Visit 2 is dependent on the dosing schedule for the assigned group.

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

1.3.3. Stage 3 Cohort(s)

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Safety Telephone Contact**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform physical examination	X							
Measure vital signs	X							
Perform urine pregnancy test (if appropriate)	X	X						
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Measure temperature (body)	X	X						
Review temporary delay criteria	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Obtain randomization number and study intervention allocation	X							
Collect blood sample for immunogenicity assessment	~50 mL		~50 mL		~50 mL	~50 mL		~50 mL
Obtain nasal (midturbinate) swab	X	X					X	

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Safety Telephone Contact**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Administer study intervention	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Provide participant with 7-day e-diary, thermometer, and measuring device	X	X						
Review e-diary data (daily review is optimal during the active diary period)	⟷	⟷						
Review ongoing e-diary symptoms and obtain stop dates		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application			X					
Telephone contact				X				
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviation: e-diary = electronic diary.

a. The window for Visit 2 is dependent on the dosing schedule(s) selected for the Stage 3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy adults.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, immunogenicity, and potential efficacy of 4 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19 in healthy adults. There are currently no vaccines to prevent infection with SARS-CoV-2 or antiviral drugs to treat COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Four SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines utilizing different RNA formats will be evaluated in this study. Each vaccine candidate is based on 1 of 3 RNA platforms: unmodified messenger RNA (uRNA), nucleoside-modified messenger RNA (modRNA), or self-amplifying messenger RNA (saRNA). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor binding domain (RBD) (version 5). The 4 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

- **BNT162a1** (variant RBL063.3): non–nucleoside-modified uridine-containing messenger RNA (uRNA) with high intrinsic adjuvanticity, encoding the RBD.
- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.
- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above but encoding P2 S.
- **BNT162c2** (variant RBP020.3): self-amplifying messenger RNA (saRNA) encoding the RBD, in which higher amounts of protein per injected RNA template can be produced.

2.2.1. Clinical Overview

BNT162 vaccines have not been administered to humans before and thus there are no previous clinical data with these specific vaccines. However, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines are expected to have a favorable safety profile with mild, localized, and transient effects.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there are currently no data available from clinical trials on the use of BNT162 vaccines in humans, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, support a favorable risk/benefit profile. Anticipated AEs after vaccination are expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates support initiation of this Phase 1/2 clinical study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the investigator's brochure (IB), which is the SRSD for this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The study design includes the use of sentinel cohorts and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of an e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place for sentinel cohorts. The first 5 sentinel-cohort participants in each group will be observed for 4 hours after vaccination to assess any immediate AEs.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The study design includes the use of sentinel cohorts and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC and DMC will also review safety data throughout the study. Stopping rules are also in place for sentinel cohorts. The first 5 sentinel cohort participants in each group will be observed for 4 hours after vaccination to assess any immediate AEs.
Potential for COVID-19 disease enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	The study excludes participants with likely previous or current COVID-19. All participants are followed for SARS-CoV-2 antigen-specific antibody and SARS-CoV-2–specific WT serum neutralizing titers, and COVID-19 illness, including markers of severity.
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of a potentially efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic and antibody testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, in sentinel cohorts from Stage 1, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: ***Stage 1 Sentinel Cohorts:*** 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts:*** 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 3 Cohort(s):*** 1, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point	SARS-CoV-2–specific WT serum neutralizing titers
	• Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination	
	• Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	
	• Geometric mean concentrations (GMCs) at each time point	SARS-CoV-2-spike protein–specific binding antibody levels and RBD-specific binding antibody levels
	• GMFR from prior to first dose of study intervention to each subsequent time point	
	• Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2–specific WT serum neutralizing titers to the geometric mean of SARS-CoV-2–specific binding antibody levels at each time point	• SARS-CoV2–specific WT serum neutralizing titers • SARS-CoV-2-spike protein–specific binding antibody levels • SARS-CoV-2 RBD–specific binding antibody levels
To evaluate the efficacy of prophylactic BNT162 vaccines against confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants) following receipt of the last dose of study intervention: 100 × (1 – infection rate ratio) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
To describe the relationship between SARS-CoV-2 serological parameters and: • NAAT-confirmed COVID-19 • Symptomatic SARS-CoV-2 infection • Asymptomatic SARS-CoV-2 infection		Nonvaccine antigen SARS-CoV-2 antibody levels

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1/2, randomized, placebo-controlled, observer-blind, dose-finding, and vaccine candidate–selection study in healthy adults.

The study will evaluate the safety, tolerability, immunogenicity, and potential efficacy of up to 4 different SARS-CoV-2 RNA vaccine candidates against COVID-19:

- As a 2-dose (separated by 21 or 60 days) or single-dose schedule
- At up to 3 different dose levels
- In 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age])

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study consists of 3 stages. Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3: a final candidate/dose large-scale stage. These stages, and the progression between them, are detailed in the schema (Section 1.2).

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Stage 1 and Stage 2.

4.1.1. Stage 1

Each group (vaccine candidate/dose level/age group/number of doses) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo. On Day 22, those in 2-dose groups will receive the same vaccine they received on Day 1; for those in single-dose groups, all will receive placebo. Full details of all potential groups in Stage 1 may be found in Table 1.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

For each vaccine candidate/dose level/age group, the 15 participants randomized into each 2-dose group will comprise a sentinel cohort, to which the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment:
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level

Groups of participants 65 to 85 years of age will not be started until safety and immunogenicity data for the same vaccine candidate/dose level have been deemed acceptable in the 18- to 55-year age cohort by the IRC.

Once the IRC has selected a vaccine candidate/dose level to proceed into Stage 2, for each age cohort, 2 additional groups will be enrolled into Stage 1 for that vaccine candidate/dose level:

- A 2-dose group, with the 2 doses administered 60 days apart rather than 21
- A 1-dose group

In this stage, assuming 2 dose levels are selected following the initial dose escalation, up to 56 potential groups are foreseen; if all groups are fully enrolled, this corresponds to a total of 840 participants.

4.1.2. Stage 2

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 or more groups (vaccine candidate/dose level) may be selected to proceed into Stage 2. Participants in this stage will be 18 to 85 years of age, stratified equally: 18 to 55 or 56 to 85 years. Commencement of each age stratum will be dependent upon satisfactory safety and immunogenicity data from the 18- to 55-year and 65- to 85-year groups from Stage 1, respectively. It is therefore possible that the 2 age strata may not start concurrently.

In each group selected for Stage 2, it is intended that 225 participants will be randomized in a 4:1 ratio to receive active vaccine (180 participants) or placebo (45 participants).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

4.1.3. Stage 3

On the basis of safety and/or immunogenicity data generated during the course of this study and/or the BioNTech study conducted in Germany (BNT162-01), 1 group may be selected to proceed into Stage 3. Participants in this stage will be 18 to 85 years of age, stratified equally: 18 to 55 years or 56 to 85 years. As in Stage 2, it is possible that the 2 age strata may not start concurrently.

The vaccine candidate/dose level selected for Stage 3 will comprise 3000 participants. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Stage 1 and Stage 2 dosing arms that are not evaluated in Stage 3.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences respiratory symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data are not currently available to experimentally validate the dose selection and initial starting dose. Therefore, the planned starting doses of 3 µg (for BNT162a1 and BNT162c2) and 10 µg (for BNT162b1 and BNT162b2) in this study are based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components (uRNA, modRNA, saRNA), with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it is expected that doses in the 1- to 5-µg range will be immunogenic and induce neutralizing antibodies; however, it is anticipated that 3- to 10-fold higher doses will likely

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it is expected that doses of up to 100 µg will be well tolerated.

Taken together, the planned starting doses in this study in healthy participants are considered to be safe, but still sufficient to induce an antiviral immune response.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Stages 1 and 2 in groups that do not proceed to Stage 3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, 65 and 85 years, inclusive, or 18 and 85 years, inclusive, at randomization (dependent upon study stage).
    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Healthy participants who are determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.

Informed Consent:

4. Capable of giving personal signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

5. **Stages 1 and 2 only:** Previous clinical or microbiological diagnosis of COVID-19.

6. **Sentinel participants in Stage 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - BMI >30 kg/m^2
    - Anticipating the need for immunosuppressive treatment within the next 6 months

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

7. **Sentinel participants in Stage 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

15. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

16. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

17. **Sentinel participants in Stage 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

18. **Sentinel participants in Stage 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

19. **Sentinel participants in Stage 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

20. **Sentinel participants in Stage 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

21. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
   - New or increased cough;
   - New or increased shortness of breath;
   - New or increased sore throat;
   - New or increased wheezing;
   - New or increased sputum production;
   - New or increased nasal congestion;
   - New or increased nasal discharge;
   - Loss of taste/smell.
2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.
3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.
4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study may evaluate 2-dose (separated by 21 or 60 days) and single-dose schedules of 3 different dose levels of 4 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age]). These 4 investigational RNA

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

vaccine candidates, with the addition of saline placebo, are the 5 potential study interventions that may be administered to a study participant:

- BNT162a1 (RNA-LNP vaccine utilizing uRNA and encoding the RBD): 3 µg, 10 µg, 30 µg
- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 30 µg, 100 µg
- BNT162c2 (BNT162 RNA-LNP vaccine utilizing saRNA and encoding the RBD): 3 µg, 10 µg, 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

A list of all potential groups in the Stage 1 are shown in Table 1. Each of these groups may or may not progress to the later stages of the study.

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
2-Dose Groups (Sentinel Cohorts)			**Day 1**			**Day 22**		
a-3-2-Y (Sentinel) [uRNA 3 µg (2 doses)]	15	18 to 55	BNT162a1 Placebo	3 µg	(n=12) (n=3)	BNT162a1 Placebo	3 µg	(n=12) (n=3)
a-10-2-Y (Sentinel) [uRNA 10 µg (2 doses)]	15	18 to 55	BNT162a1 Placebo	10 µg	(n=12) (n=3)	BNT162a1 Placebo	10 µg	(n=12) (n=3)
a-30-2-Y (Sentinel) [uRNA 30 µg (2 doses)]	15	18 to 55	BNT162a1 Placebo	30 µg	(n=12) (n=3)	BNT162a1 Placebo	30 µg	(n=12) (n=3)
b1-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	10 µg	(n=12) (n=3)	BNT162b1 Placebo	10 µg	(n=12) (n=3)
b1-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	30 µg	(n=12) (n=3)	BNT162b1 Placebo	30 µg	(n=12) (n=3)
b1-100-2-Y (Sentinel) [modRNA 100 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	100 µg	(n=12) (n=3)	BNT162b1 Placebo	100 µg	(n=12) (n=3)
b2-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	10 µg	(n=12) (n=3)	BNT162b2 Placebo	10 µg	(n=12) (n=3)
b2-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	30 µg	(n=12) (n=3)	BNT162b2 Placebo	30 µg	(n=12) (n=3)
b2-100-2-Y (Sentinel) [modRNA 100 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	100 µg	(n=12) (n=3)	BNT162b2 Placebo	100 µg	(n=12) (n=3)

This document may be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
c-3-2-Y (Sentinel) [saRNA 3 µg (2 doses)]	15	18 to 55	BNT162c2 Placebo	3 µg	(n=12) (n=3)	BNT162c2 Placebo	3 µg	(n=12) (n=3)
c-10-2-Y (Sentinel) [saRNA 10 µg (2 doses)]	15	18 to 55	BNT162c2 Placebo	10 µg	(n=12) (n=3)	BNT162c2 Placebo	10 µg	(n=12) (n=3)
c-30-2-Y (Sentinel) [saRNA 30 µg (2 doses)]	15	18 to 55	BNT162c2 Placebo	30 µg	(n=12) (n=3)	BNT162c2 Placebo	30 µg	(n=12) (n=3)
a-3-2-O (Sentinel) [uRNA 3 µg (2 doses)]	15	65 to 85	BNT162a1 Placebo	3 µg	(n=12) (n=3)	BNT162a1 Placebo	3 µg	(n=12) (n=3)
a-10-2-O (Sentinel) [uRNA 10 µg (2 doses)]	15	65 to 85	BNT162a1 Placebo	10 µg	(n=12) (n=3)	BNT162a1 Placebo	10 µg	(n=12) (n=3)
a-30-2-O (Sentinel) [uRNA 30 µg (2 doses)]	15	65 to 85	BNT162a1 Placebo	30 µg	(n=12) (n=3)	BNT162a1 Placebo	30 µg	(n=12) (n=3)
b1-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	10 µg	(n=12) (n=3)	BNT162b1 Placebo	10 µg	(n=12) (n=3)
b1-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	30 µg	(n=12) (n=3)	BNT162b1 Placebo	30 µg	(n=12) (n=3)
b1-100-2-O (Sentinel) [modRNA 100 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	100 µg	(n=12) (n=3)	BNT162b1 Placebo	100 µg	(n=12) (n=3)
b2-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	10 µg	(n=12) (n=3)	BNT162b2 Placebo	10 µg	(n=12) (n=3)
b2-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	30 µg	(n=12) (n=3)	BNT162b2 Placebo	30 µg	(n=12) (n=3)
b2-100-2-O (Sentinel) [modRNA 100 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	100 µg	(n=12) (n=3)	BNT162b2 Placebo	100 µg	(n=12) (n=3)
c-3-2-O (Sentinel) [saRNA 3 µg (2 doses)]	15	65 to 85	BNT162c2 Placebo	3 µg	(n=12) (n=3)	BNT162c2 Placebo	3 µg	(n=12) (n=3)
c-10-2-O (Sentinel) [saRNA 10 µg (2 doses)]	15	65 to 85	BNT162c2 Placebo	10 µg	(n=12) (n=3)	BNT162c2 Placebo	10 µg	(n=12) (n=3)
c-30-2-O (Sentinel) [saRNA 30 µg (2 doses)]	15	65 to 85	BNT162c2 Placebo	30 µg	(n=12) (n=3)	BNT162c2 Placebo	30 µg	(n=12) (n=3)
Single-Dose Groups			**Day 1**			**Day 22**		
a-x-1-Y [uRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162a1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b1-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b2-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
c-x-1-Y [saRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162c2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
a-x-1-O [uRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162a1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b1-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b2-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
c-x-1-O [saRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162c2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
2-Dose Groups (Longer Schedule)			**Day 1**			**Day 61**		
a-x-2L-Y [uRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162a1 Placebo	TBD	(n=12) (n=3)	BNT162a1 Placebo	TBD	(n=12) (n=3)
b1-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b1 Placebo	TBD	(n=12) (n=3)	BNT162b1 Placebo	TBD	(n=12) (n=3)
b2-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b2 Placebo	TBD	(n=12) (n=3)	BNT162b2 Placebo	TBD	(n=12) (n=3)
c-x-2L-Y [saRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162c2 Placebo	TBD	(n=12) (n=3)	BNT162c2 Placebo	TBD	(n=12) (n=3)
a-x-2L-O [uRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162a1 Placebo	TBD	(n=12) (n=3)	BNT162a1 Placebo	TBD	(n=12) (n=3)
b1-x-2L-O [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162b1 Placebo	TBD	(n=12) (n=3)	BNT162b1 Placebo	TBD	(n=12) (n=3)
b2-x-2L-O [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162b2 Placebo	TBD	(n=12) (n=3)	BNT162b2 Placebo	TBD	(n=12) (n=3)
c-x-2L-O [saRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162c2 Placebo	TBD	(n=12) (n=3)	BNT162c2 Placebo	TBD	(n=12) (n=3)

Abbreviations: modRNA = nucleoside-modified messenger ribonucleic acid; saRNA = self-amplifying messenger ribonucleic acid; TBD = to be determined; uRNA = uridine-containing messenger ribonucleic acid.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

6.1. Study Intervention(s) Administered

Intervention Name	BNT162a1 (BNT 162 RNA-LNP vaccine utilizing uRNA)	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162c2 (BNT162 RNA-LNP vaccine utilizing saRNA	Saline placebo
Type	Vaccine	Vaccine	Vaccine	Vaccine	Placebo
Dose Formulation	uRNA	modRNA	modRNA	saRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)	3-, 10-, 30-µg	10-, 30-, 100-µg	10-, 30-, 100-µg	3-, 10-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement

6.1.1. Administration

Participants will receive 1 dose (0.5 mL) of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Stage 1 sentinel cohort participants, Visits 1 and 2 for all other participants) in accordance with the study's SoA.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emaeuropa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Stage 1 and in Stage 2. Sponsor staff will be blinded to study intervention allocation in Stage 3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study.

Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate). Unblinded clinician(s) who are not direct members of the study team will review unblinded protocol deviations.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Stage 1 sentinel cohorts, Visit 5 for Stage 1 nonsentinel cohorts and Stage 2 participants, and Visit 4 for Stage 3 participants).

- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- In addition, for participants enrolled in the Stage 1 sentinel cohorts, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 for Stage 1 sentinel cohorts, Visit 4 for Stage 1 nonsentinel cohorts and Stage 2 participants, and Visit 3 for Stage 3 participants).

Receipt of blood/plasma products or immunoglobulins within 6 months before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled, topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

6.6. Dose Modification

Individual participant dose modifications will not be made in this study.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria).

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

The total blood sampling volume for individual participants in this study is approximately 530 mL for participants in the Stage 1 sentinel cohorts; 350 mL for participants in the Stage 1 nonsentinel cohorts and Stage 2 participants; and 200 mL for Stage 3 participants. Additionally, 50 mL of blood will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, a telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. Four definitions of potential SARS-CoV-2–related cases will be considered:

- Centrally confirmed COVID-19: presence of at least 1 symptom described in Section 8.13 and SARS-CoV-2 NAAT positive at central laboratory
- Locally confirmed COVID-19: presence of at least 1 symptom described in Section 8.13 and investigator-confirmed SARS-CoV-2 NAAT positive at a local testing facility
- Centrally confirmed symptomatic seroconversion to SARS-CoV-2 (exploratory): presence of at least 1 symptom described in Section 8.13 and a positive nonvaccine antigen SARS-CoV-2 antibody result in a participant whose most recent prior nonvaccine antigen SARS-CoV-2 antibody result was negative
- Centrally confirmed asymptomatic seroconversion to SARS-CoV-2 (exploratory): positive nonvaccine antigen SARS-CoV-2 antibody result in a participant with a prior nonvaccine antigen SARS-CoV-2 antibody result was negative

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2–specific WT serum neutralization assay
- SARS-CoV-2-spike (S) protein–specific IgG direct Luminex immunoassay
- SARS-CoV-2 RBD–specific IgG direct Luminex immunoassay

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Nonvaccine antigen (NVA) Ig direct Luminex immunoassay. The NVA will include a SARS-CoV-2 target antigen that is not derived from the S glycoprotein, most likely an antigen derived from the SARS-CoV-2 nucleoprotein.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Stage 1 sentinel group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2.

8.2.1. Clinical Safety Laboratory Assessments (Sentinel-Cohort Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

This document cannot be used to support any marketing authorisation application and any extension or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.2. Electronic Diary

Participants will be required to complete an e-diary through an application installed on a provisioned device or on the participant's own personal device. The participant will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. The e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

8.2.2.2. Local Reactions

During the e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary. If a local reaction persists beyond the end of the e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 2. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 2.

If a Grade 3 local reaction is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

8.2.2.3. Systemic Events

During the e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 3.

If a Grade 3 systemic event is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the e-diary in the evening daily during the e-diary reporting period. It will also be collected at any time during the e-diary data collection periods when fever is suspected. Fever is

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 4.

If a fever of ≥39.0°C (102.1°F) is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 4. Scale for Fever

38.0-38.4°C (100.4-101.1°F)
38.5-38.9°C (101.2-102.0°F)
39.0-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Stopping Rules

The following stopping rules are in place for all Stage 1 sentinel-cohort participants, based on review of AE data and e-diary reactogenicity data. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during the Stage 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. E-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

BNT162 vaccine candidates will be evaluated for contribution to stopping rules individually; vaccine candidate dose levels and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event within 7 days after vaccination that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement within 7 days after vaccination that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) within 21 days after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19 disease.

8.2.3.1. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC and DMC have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 Disease

As this is a sponsor open-label study during Stages 1 and 2, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment.

Participants in all stages of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13). All NAAT-confirmed cases will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6). In addition, instances of symptomatic and asymptomatic seroconversion to SARS-CoV-2 (see Section 8.1) will be reviewed.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review. Since the DMC is able to review unblinded information, it will also be able to compare cases in active vaccine and placebo recipients in Stage 3 (when sponsor staff will be blinded).

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Stage 1 sentinel-cohort participants, Visit 4 for Stage 1 nonsentinel participants and Stage 2 participants, and Visit 3 for Stage 3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Stage 1 sentinel-cohort participants, Visit 5 for Stage 1 nonsentinel cohort participants and Stage 2 participants, and Visit 4 for Stage 3 participants).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccines SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccines SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccines SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are recorded on the CRF. AEs and SAEs that begin after obtaining informed consent but before the start of study intervention will be recorded on the Medical

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

History/Current Medical Conditions section of the CRF, not the AE section. AEs and SAEs that begin after the start of study intervention are recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
  - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccines SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccines SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccines SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

CRF. However, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccines SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

8.3.6. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccines SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

8.11.1. Stage 1 Sentinel Cohorts

8.11.1.1. Screening: (0 to 14 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Collect a blood sample (approximately 20 mL) for serological assessment of prior COVID-19 infection.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.5.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.

- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Perform physical examination including vital signs (body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- The first 5 participants vaccinated in each Stage 1 sentinel group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Explain the e-diary technologies available for this study, and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.

- Perform physical examination including vital signs (body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Perform physical examination including vital signs (body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Perform physical examination including vital signs (body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.

- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.

- Perform physical examination including vital signs (body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Discuss contraceptive use as described in Section 10.4.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Perform physical examination including vital signs (body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Schedule an appointment for the participant to return for the next study visit.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

8.11.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study, and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)

The window for Visit 2 is dependent on the dosing schedule for the assigned group.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.

- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy (see Section 7.1).

- Measure the participant's body temperature.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Obtain a nasal (midturbinate) swab (collected by site staff).

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

8.11.2.3. Visit 3 – 2-Week Follow-up Visit: (12 to 16 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.4. Visit 4 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.5. Visit 5 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.7. Visit 7 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.3. Stage 3 Cohort(s)

8.11.3.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study, and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.3.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)

The window for Visit 2 is dependent on the dosing schedule(s) selected for Stage 3.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.3.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- The investigator or an authorized designee completes the CRFs.

8.11.3.4. Visit 4 – 6-Month Safety Telephone Contact: (154 to 168 Days After Visit 2)

- Contact the participant by telephone in order to obtain the following information.
- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.3.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.3.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Disease Surveillance (All Participants)

If a participant experiences any of the following, he or she is instructed to contact the site immediately, and if confirmed, participate in a telehealth visit as soon as possible, optimally within 3 days of symptom onset. Note that this does not substitute for a participant's routine medical care. Therefore participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- New or increased sore throat;
- New or increased wheezing;
- New or increased sputum production;
- New or increased nasal congestion;
- New or increased nasal discharge;
- Loss of taste/smell.

8.13.1. Potential COVID-19 Illness Telehealth Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This telehealth visit is expected to involve the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

As a participant's COVID-19 illness may evolve over time, several telehealth contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory. The result from this swab will be provided to the site once it is available, but this will not be in real time, and cannot be relied upon to direct clinical care. Therefore, the participant should be encouraged to seek care, if appropriate, from his or her usual provider.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
  - Symptoms
  - Clinical diagnosis
  - Local laboratory COVID-19 test result
  - Full blood count
  - C-reactive protein
  - Number and type of any healthcare contact; duration of hospitalization and intensive care unit stay
  - Need for oxygen therapy
  - Need for ventilation
- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

9.1.2. Statistical Hypotheses

At the end of Stage 3, the vaccine efficacy (VE) will be evaluated. VE is defined as VE = 100 × (1 – IRR), where IRR is the infection rate ratio, the calculated ratio of the COVID-19 infection rate in the active vaccine group to the incidence rate in the placebo group. The efficacy hypothesis is:

H_0: VE ≤20% vs H_a: VE >20%

where H_0 and H_a represent null hypothesis and alternative hypothesis. For participants with multiple infections, only the first infection will contribute to the VE calculation in the hypothesis test.

The efficacy will be demonstrated if the null hypothesis VE ≤20% is rejected at the 0.025 significance level, that is, when the lower limit of the 2-sided 95% CI for VE is >20%, which is derived using the Clopper-Pearson method as described by Agresti.[9]

9.2. Sample Size Determination

The study sample size for the first 2 stages of the study is not based on any statistical hypothesis testing. Stage 1 will comprise 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; up to 56 potential groups are foreseen; if all groups are fully enrolled, assuming 2 dose levels are selected following the initial dose escalation, this corresponds to a total of 840 participants. Stage 2 will include 1 or more vaccine groups selected from Stage 1, and 225 participants will be randomized per selected vaccine candidate in a 4:1 ratio to receive active vaccine (180 participants) or placebo (45 participants).

For Stage 3, for the selected vaccine candidate/dose level, with assumptions of a true vaccine efficacy (VE) of 70%, 53 cases of COVID-19 will provide 90% power to conclude true VE >20%. This would be achieved with 3000 participants per group (1:1 randomization ratio), based on the assumption of a 1.7% incidence rate in the placebo group, and 20% of the participants being non-evaluable.

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=3000
0.10%	0.01	0.04	0.16	0.95
0.50%	0.06	0.20	0.59	>0.99
1.00%	0.11	0.36	0.84	>0.99
2.00%	0.22	0.60	0.97	>0.99
3.00%	0.31	0.75	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	All eligible randomized participants who are 18 to 85 years of age (stratified by 18 to 55 and 56 to 85) (inclusive) on the day of first vaccination, receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result 21 days after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other major protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who are 18 to 85 years of age (stratified by 18 to 55 and 56 to 85) (inclusive) on the day of first vaccination, receive 2 randomized vaccinations within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other major protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result 21 days after Dose 1.
Dose 2 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result 14 days after Dose 2.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Population	Description
Evaluable efficacy	All eligible randomized participants who are 18 to 85 years of age (inclusive) on the day of first vaccination, receive 2 vaccinations as randomized within the predefined window, have the efficacy measurement after Dose 2, and have no other major protocol deviations as determined by the clinician.
All-available efficacy	All eligible randomized participants who are 18 to 85 years of age (inclusive) on the day of first vaccination, receive at least 1 vaccination, and have the efficacy measurement after Dose 2.
Safety	All randomized participants who receive at least 1 dose of the study intervention and have safety data assessed after any dose.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific binding antibody levels and RBD-specific binding antibody levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product (active/placebo) within each group before vaccination and at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 12, and 24 months after Dose 2 Geometric means and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on the t-distribution, and then exponentiating the results. **GMFRs of SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific antibody levels and RBD-specific binding levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and transformed back

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Endpoint	Statistical Analysis Methods
	to the original scale. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and transforming the limits back to the original scale. **Percentage of participants with ≥4-fold rise in SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific antibody levels and RBD-specific binding levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2–specific WT serum neutralizing titer fold rise to SARS-CoV-2-spike protein–specific antibody and SARS-CoV-2 RBD–specific binding antibody** For SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific binding antibody levels and RBD-specific binding antibody levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 Cohort(s): 1, 12, and 24 months after Dose 2

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Endpoint	Statistical Analysis Methods
	GMRs will be limited to participants with nonmissing values for both SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific antibody/SARS-CoV-2 RBD–specific binding antibody at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2–specific WT serum neutralizing titers minus SARS-CoV-2-spike protein–specific antibody for each participant) and transformed back to the original scale. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and transforming the limits back to the original scale. The same analysis methods will be applied to the immunogenicity endpoints in Stages 2 and 3. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Tertiary/ exploratory immunogenicity	**Correlation of an RT-PCR–confirmed COVID-19 infection and seropositivity/seroconversion measured by nonvaccine antigen SARS-CoV-2 antibody** If sufficient data are collected, percentages (and 2-sided 95% CIs) of participants with confirmed COVID-19 and nonvaccine antigen SARS-CoV-2 antibody levels after Dose 1 and after Dose 2 will be provided. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2–specific WT serum neutralizing titers, SARS-CoV-2-spike protein–specific antibody, and RBD-specific binding antibody after Dose 1 and after Dose 2.

9.4.2. Efficacy Analyses

The statistical analysis of efficacy will be based on the evaluable efficacy population (primary analysis) and the all-available efficacy population as defined in Section 9.3.

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
Secondary efficacy	**Ratio of COVID-19 incidence per 1000 person-years of follow-up for the active vaccine group to the placebo group** Vaccine efficacy will be estimated by 100 × (1 – IRR), where IRR is the infection rate ratio, the calculated ratio of COVID-19 infection incidence per 1000 person-years follow-up in the active vaccine group to the corresponding incidence in the placebo group after 2 doses. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. For the primary analysis, missing efficacy data will not be imputed. A sensitivity analysis may be performed by imputing missing values; details will be provided in the SAP.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	• Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. • For Stage 1 sentinel cohorts, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. • AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

Endpoint	Statistical Analysis Methods
	defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. • Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. • SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after last dose will be provided for each vaccine group. • The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	• Not applicable (N/A)
Exploratory	• N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2–specific WT serum neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the SARS-CoV-2 spike protein–specific binding antibody level at the postvaccination time point to the corresponding antibody level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the SARS-CoV-2 RBD–specific binding antibody level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

9.5. Interim Analyses

No formal interim analysis is planned in this study. As this is a sponsor open-label study during Stages 1 and 2, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 3 weeks after Dose 2 for Stage 1.
- Complete safety and immunogenicity analysis approximately 3 weeks after Dose 2 for Stage 2.
- Complete safety, immunogenicity, and efficacy analysis after complete data are available for all participants for Stage 3.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC and a DMC. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC will include:

- Review of safety data to permit dose escalations
- Review of safety data in the case of a stopping rule being met
- Review of safety and immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate(s)/dose level(s), and schedule(s) to proceed into Stage 2
  - Select vaccine candidate(s)/dose level(s), and schedule(s) to proceed into Stage 3
- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

- Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses

- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule

- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule

- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 6).

Table 6. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Female) change from baseline value - g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hemoglobin (Male) change from baseline value – g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Table 6. Laboratory Abnormality Grading Scale

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 99,000	<25,000
Chemistry	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
www.ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccines SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccines SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccines SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and EDP supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccines SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccines SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccines SAE Report Form
• Facsimile transmission of the Vaccines SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccines SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccines SAE Report Form pages within the designated reporting time frames.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

   - Oral;
   - Intravaginal;
   - Transdermal;
   - Injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - Oral;
   - Injectable.

8. Sexual abstinence:

   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
emc.europa.eu

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use application
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof

Abbreviation	Term
HBc Ab	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	infection rate ratio
IRT	interactive response technology
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
modRNA	nucleoside-modified messenger ribonucleic acid
N/A	not applicable
NAAT	nucleic acid amplification test
NVA	nonvaccine antigen
P2 S	SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein

This document cannot be used to support any marketing authorization application and any extensions or variations thereof

090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Abbreviation	Term
PCR	polymerase chain reaction
PI	principal investigator
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal
uRNA	uridine-containing messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WT	wild type

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 March 2020. Accessed: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020: 10 pages.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): therapeutic options. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Accessed: 12 Apr 2020.

4 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

5 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

6 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 March 2020.

7 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine. 2019;37(25):3326-34.

8 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

9 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, editor. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

10 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)

Document Approval Record

Document Name:	C4591001 Clinical Protocol, 15 Apr 2020
Document Title:	A PHASE 1/2, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO DESCRIBE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND POTENTIAL EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY ADULTS

Signed By:	Date(GMT)	Signing Capacity
PPD	17-Apr-2020 09:47:05	Business Line Approver
PPD	17-Apr-2020 12:10:48	Final Approval

This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
090177e193424de3\Approved\Approved On: 17-Apr-2020 12:10 (GMT)